A rapid and systematic review of the clinical and cost effectiveness of bupropion SR and nicotine replacement therapy (NRT) for smoking cessation

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CONFLICTS OF INTEREST

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None

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The views expressed in this report are those of the authors and not necessarily of the NHS R&D Programme. Any errors are the responsibility of the authors.

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SUMMARY

Aims of the review

This review aims to address the effectiveness, cost-effectiveness and adverse effects of bupropion SR (Zyban®) and nicotine replacement therapy (NRT) for smoking cessation. It does not consider the effects of therapy in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit.

Background

The health hazards of smoking are significant and well established. Giving up smoking is difficult and therefore needs to be treated as a chronic, but potentially curable illness. NRT and bupropion SR (Zyban®) are two pharmacological agents available to aid smokers in their attempts to achieve smoking cessation.

Methods

Search strategy

Twenty-six electronic databases and Internet resources were searched from inception to May 2001. In addition the bibliographies of retrieved articles and submissions received from the manufacturers were searched.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and abstracts for relevance and made final decisions on the inclusion/exclusion criteria of studies based on full paper copies of manuscripts. Studies were assessed according to pre-defined criteria. Any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted. Only systematic reviews and newly identified randomised controlled trials (RCTs) of bupropion slow-release formulation (SR) (used alone or as part of a combination therapy with motivational support or motivational support and NRT), or any type of NRT were included in the review of clinical effectiveness. Participants included smokers of any age or gender and studies had to report abstinence (preferably continued rather than point abstinence) as an outcome measure. In addition, the assessment of adverse effects also included non-randomised controlled trials, case-controlled studies, uncontrolled studies and surveillance studies whose primary objective was the investigation of the adverse effect, tolerability or safety of bupropion SR or immediate-release (IR) and/or NRT. Case reports and case series

were also documented. The economic assessment included evaluations of the cost-effectiveness or cost-utility of bupropion SR and/or NRT.

Data extraction strategy

Data were extracted into an Access database by one reviewer and checked by a second reviewer. Any disagreements were resolved through discussion.

Quality assessment strategy

The quality of each study was assessed using pre-defined criteria specified according to study design. The assessment was performed by one reviewer and checked by a second reviewer. Disagreements were resolved through consensus and if necessary a third reviewer was consulted.

Analysis strategy

Study details, validity and data were reported in structured tables and discussed in the text of the review. For the assessment of clinical effectiveness, where available and appropriate, pooled estimates of effect in the form of odds ratios from systematic reviews are presented. Sub-group and sensitivity analyses are reported where data are available. For the assessment of adverse events and safety the summary was mainly a narrative one. For the assessment of cost effectiveness evaluations were grouped according to design.

Results

Included studies

A total of 157 studies were included in the review. These comprised three systematic reviews and 13 individual studies of effectiveness; four systematic reviews and 112 individual studies relating adverse events and safety; and 17 economic studies.

Quality of clinical effectiveness data

The quality of the systematic reviews and individual RCTs included in the review was good.

Quality of adverse effects data

The nature and quality of the adverse effect and safety data were very variable. In particular, many of the studies were uncontrolled, with all the inherent weaknesses of such studies. Furthermore many of the uncontrolled studies were small, but many of

the larger ones suffered from poor quality of the reporting. Interpretation of surveillance data was limited by a lack of information on the size of the population treated.

Assessment of clinical effectiveness

The effectiveness of NRT as an aid to smoking cessation has been thoroughly investigated. The evidence indicates unequivocally that NRT as an aid to smoking cessation is more effective than placebo. The majority of the data come from studies with NRT gum and NRT patch. Despite this, there are no data to indicate that other forms of NRT are less efficacious. There are no data to indicate sub-group differences in the response to NRT.

There is clear evidence that bupropion SR is more effective than placebo. There is evidence from single sub-group populations that bupropion SR is as effective in smokers with chronic obstructive pulmonary disease (COPD), cardiovascular disease, and those who have failed in the past to achieve abstinence with bupropion SR, as in the general smoking population.

Evidence to support the superiority of bupropion SR over NRT for smoking cessation is relatively weak, with one double-blind study indicating that the NRT patch is less effective than bupropion SR and another unblinded study finding no difference between NRT gum and bupropion SR. Further double-blind RCTs are required.

Assessment of adverse events and safety

Overall, the incidence of adverse events with NRT is very low. The main concern regards potential adverse cardiovascular effects i.e. the same harmful effects that are the driving force behind needing to 'treat' smoking as a chronic illness. There is strong evidence that the effects of nicotine acquired through NRT are no different from those of smoking-derived nicotine. Evidence suggests that the main problem with NRT is that its use can delay the reversal of the adverse effects of smoking normally associated with smoking cessation. There is evidence to suggest that the abuse potential of NRT is low.

There is only very limited overlap of adverse symptoms associated with the different types of NRT. Thus, the qualitative differences of the adverse effects associated with the different types of NRT will determine their effectiveness in different individuals.

None of the common adverse events of bupropion (Rash and pruritus, irritability, insomnia; dry mouth; headache; tremor; urticaria, rash; urticaria; insomnia; headache; dry mouth; and tremor) reported in this review are newly identified. The adverse events resulting in withdrawal from treatment with bupropion SR are the same as those with the IR formulation (skin disorders (mainly rash), insomnia, tremor, headache, dry mouth and anxiety) with the exception of motor disturbances, psychological problems, drowsiness, weight loss, headache/nasal congestion, thinking difficulties, dizziness, and tachycardia/palpitations. Such differences might be due to differences in dose, duration of treatment and differences in response between depressed and non-depressed patients. Significantly, the side effect profile of SR does appear to be better than that of IR.

As was already recognised, this review has identified seizure as the most significant and important potential adverse effect of bupropion SR.The crude incidence of seizure is lower with the SR than with the IR formulation, however, the evidence demonstrates that even in populations screened to exclude those at risk, seizures can occur. Significantly, no RCT of bupropion SR in smoking cessation has reported any seizures. This may be related to stricter screening in the clinical trial setting than occurs in clinical practice.

Assessment of cost effectiveness

Published economic studies of smoking cessation have adopted different methods and assumptions for estimating effectiveness and costs. However, the results of existing economic evaluations consistently indicate that smoking cessation interventions are relatively cost-effective in terms of cost per life-year saved. An assessment of results from existing studies suggests that the number of life-years saved per quitter ranges from 1.0 to 3.0. Adding NRT to current practice is cost-effective, with a relatively low (under £1k) incremental cost per quitter. No published studies have evaluated the relative cost-effectiveness of bupropion SR for smoking cessation.

A decision analysis model has been built to compare the cost-effectiveness of four smoking cessation interventions: (1) advice or counselling only (including GP advice and more intensive counselling by other health professionals), (2) advice plus NRT, (3) advice plus bupropion SR, and (4) advice plus NRT and bupropion SR.

The results of this decision analysis modelling are broadly similar to that of previous studies. NRT and/or bupropion SR as smoking cessation interventions are cost-effective as compared with many accepted healthcare interventions. According to our estimates, the incremental cost per life-years saved is about £1,000-2,400 for NRT, £640-1,500 for bupropion SR, and £900-2,000 for NRT plus bupropion SR.

The estimated cost of the smoking cessation programme to the NHS in England and Wales would be about £67-202 million per year. Consequently, about 45,000-135,000 smokers would quit, and 90,000-270,000 life-years may be saved. The average cost per life-year is about £750 (range £500 to £1,500).

The incremental cost-effectiveness of bupropion SR is generally better than that of NRT. However, this should be interpreted cautiously because of the very limited data on the relative efficacy of bupropion SR and because the cost of bupropion SR adverse effects were not considiered in the analysis.

Conclusions

- Both NRT and bupropion SR are effective interventions to assist smoking cessation.
- The relative effectiveness of bupropion SR and NRT still needs further research.
- Information on how to maximise effectiveness in practice is still lacking, but probably involves motivational support.
- The most significant differences between NRT and bupropion SR relate to the adverse events and safety profiles of these interventions.
- Overall, the safety profile of NRT is more favourable, particularly given the small but real risk of seizure with bupropion SR.
- Irrespective of methods used or assumptions involved, the results of existing economic evaluations and the model developed in this review consistently suggest that smoking cessation interventions, including use of NRT and/or bupropion SR, are relatively cost-effective in terms of cost per life-year saved. The worst case scenarios still provide estimates of cost-effectiveness better than many other medical interventions.

LIST OF ABBREVIATIONS

ACT	abstinence-contingent treatment
ADRAC	Adverse Drug Reactions Advisory Committee
AEs	adverse events
ALA	American Lung Association
ANOVA	analysis of variance
AUC	area under the curve
b.i.d	twice a day
BMI	body mass index
BP	blood pressure
CABG	coronary-artery bypass graft
CAD	coronary artery disease
CADR	Canadian Adverse Drug Reactions
CB	cost benefit
CDC	Centre for Disease Control
CE	cost effectiveness
CHF	chronic heart failure
CI	confidence interval
CI	cardiac index
CNS	central nervous system
CO	carbon dioxide
COPD	chronic obstructive pulmonary disease
NHS CRD	NHS Centre for Reviews and Dissemination
CSFQ	Changes in Sexual Functioning Questionnaire
CU	cost utility
DBP	diastolic blood pressure
Df	degrees of freedom
DSM-III-R	Diagnostics Statistics Manual, version 3, revised
ECG	electrocardiogram
EEG	electroencephalogram
FBF	forearm blood flow
FDA	Food and Drug Administration
FEV	forced expiratory volume
FVC	forced vital capacity

FVR	forearm vascular resistance
GP	General Practitioner
GSK	Glaxo SmithKline
HAZ	health action zone
HDL	high lipid density
HEOCS	Health and Economic Consequences of Smoking
HR	heart rate
HRV	heart rate variability
IR	immediate release
ITT	intention-to-treat
LDL	low lipid density
LHS	Lung Health Study
LOCF	last observation carried forward
LVF	left ventricular function
Lys	life years
MABP	mean arterial blood pressure
MAO	monoamine oxidase
MAP	mean arterial pressure
MCA	Medicines Control Agency
MI	myocardial infarction
NA	not applicable
NHS	National Health Service
NRT	nicotine replacement therapy
NS	not significant
OR	odds ratio
OTC	over-the-counter
PAS	Pharmacist Action on Smoking
PBI	Penile brachial index
PDS	perfusion defect size
PREVENT	Economic analysis model (not defined)
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RI	resistance index
RR	relative risk
SBP	systolic blood pressure

SC	smoking cessation
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SPECT	single photon emission computed tomography
SR	sustained release
t.i.d.	three times a day
TPRI	total peripheral resistance index
YHL	years of healthy life

DEFINITIONS OF TERMS

Adverse effect

An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism, or increases the susceptibility of the organism to other chemical or biological stress.

Alopecia

Baldness/the loss of body hair.

Anaemia

An abnormally low level of red blood cells in the blood. Red blood cells are responsible for carrying oxygen around the body.

Analphylactic shock

When an abnormal response of the body to a foreign substance is so severe that it leads to profound shock and collapse, which, unless treated urgently, can cause death.

Arthralgia

Joint pain.

Angioedema

Swelling around the eyes, often associated with allergic reactions.

Case-control study

A comparison of exposure to interventions between participants with the outcomes (cases) and those without the outcome (controls).

Case report

A description of a single patient whose case displays interesting features. This is usually used to generate ideas and raise questions, rather than to answer them.

Case series

Similar to a case report, except that a number of similar cases have been observed.

Cohort study

An investigation in which a group of individuals (the cohort) is identified and followed prospectively, perhaps for many years, and their subsequent medical history recorded. The cohort may be subdivided at the onset into groups with different characteristics, for example, exposed and not exposed to some risk factor, and at some later stage a comparison made of the incidence of a particular disease in each group.

Confidence intervals

Quantifies the uncertainty in measurement. Usually reported as 95% CI, i.e. the range of values within which 95% sure that the true values for the whole population lie.

Controlled trial or study

A trial or study that compares two or more interventions: the intervention(s) of interest and the 'control' intervention(s). A 'control' intervention can be placebo, another active comparator (reference) or usual care or nothing.

Cost benefit (CB) analysis

A form of economic evaluation where both costs and benefits are expressed in the same units, usually monetary units, i.e. all of the health benefits (e.g. disability days avoided, life-years gained, medical complications avoided) are translated into monetary units. This type of analysis is not widely used in the economic evaluation of drugs or technologies, as it is often difficult to determine the cost of health benefits.

Cost effectiveness (CE) analysis

A form of economic evaluation where costs are expressed in monetary units and effectiveness is expressed in some unit of effectiveness. Units of effectiveness are usually the same as those clinical outcomes used to measure effectiveness in clinical trials or practice. When comparing two interventions the difference in cost and effectiveness between the two interventions is expressed as a cost-effectiveness ratio, with the difference in cost in the numerator and the difference in survival in the denominator.

Cost utility (CU) analysis

A special form of cost-effectiveness analysis in which utility is measured and the units of effectiveness are quality-adjusted life-years (QALYs). Utilities can be derived using various methods including the standard gamble and time tradeoff techniques which are both based on utility theory. However this form of economic evaluation has the disadvantage that utility data are often not collected in clinical trials because of the additional costs of data collection and the complex nature of the methods used in utility assessments. Cost utility analyses are important in the evaluation of cancer therapies, as such therapies are often associated with potentially serious or intolerable adverse effects.

Erythema multiforme

Red blotches of diverse appearance on hands and arms, producing lumps and vesicles or even large blebs full of fluid.

Fagerstrom score

Rating of nicotine dependance.

Hazard ratio

The hazard (the instantaneous risk of patient experiencing a particular event at a specified time point) associated with one category of patients divided by the hazard of another set of patients. The hazard ratio can be estimated at an instant or averaged over an interval.

Heterogeneous

Of differing origins or different types.

Incremental cost-effectiveness analysis

An analysis where estimates are made of the additional cost per year of life saved or gained. This type of analysis is often carried out to provide a more meaningful comparison of costs and consequences between different interventions.

Lymphocytopenia

An abnormally low level of lymphocytes in the blood. Lymphocytes are white cells which help to fight infections within the body and are responsible for producing antibodies.

Mania

A form of mental disorder characterised by great excitement.

Meta-analysis

The statistical pooling of the results of a collection or related individual studies, to increase statistical power and synthesise their findings.

Myalgia

Muscle pain.

Neuropathy

A term to describe any disorder of the neurones or nerves of the body.

Neutropenia

An abnormally low level of neutrophils in the blood. Neutrophils belong to a group of white blood cells known as granulocytes, which are important in fighting infections within the body.

Odds ratio

Odds ratio is similar to relative risk except that the denominator takes into account the number of individuals witthin the poulation that experienced the event of interest. The results of relative risk and odds ratio calculations are very similar for rare events but diverge as events become more common.

Paraesthesiae

Numbness/tingling or ‘pins and needles’ sensation of the skin.

Pruritus

Itchiness.

Psychosis

Serious disorder of the mind amounting to insanity.

QALY

An index of survival that is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality of life (QoL)

A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors which might affect their physical, mental and social well-being.

Randomised controlled trial

A controlled clinical trial in which the participants are randomly assigned to the intervention or control treatment group or are randomly assigned to the order in which an intervention and its control are received.

Relative risk

Also called the 'risk ratio'. A common way of estimating the risk of experiencing a particular effect or result. A RR > 1 means a person is estimated to be at an increased risk, while a RR < 1 means a person is apparently at decreased risk. A RR of 1.0 means there is no apparent effect on risk at all, e.g., if the RR = 4.0, the result is about 4 times as likely to happen, and 0.4 means it is 4 times less likely to happen. The RR is expressed with confidence intervals: e.g., RR 3.0 (95% CI: 2.5 - 3.8). This means the result is 3 times as likely to happen - anything from 2.5 times as likely, to 3.8 times as likely. It is statistically significant. On the other hand, RR 3.0 (95% CI: 0.5 - 8.9), means it is also estimated to be 3 times as likely, but it is not statistically significant. The chances go from half as likely to happen (0.5 a decreased chance), to nearly 9 times as likely to happen (8.9 an increased chance).

Serum sickness

A hypersensitivity reaction due to circulating antigen antibody complexes. It is characterised by fever, arthralgia and lymphadenopathy and is usually self-limiting.

Stephens-Johnson syndrome

This is a from of erythema multiforme which is characterised by annular lesions which can develop into blisters. In addition to the blisters there is severe involvement

of the eyes and mucosa, giving rise to ulceration. It is commonly a hypersensitivity reaction to drugs.

Thrombocytopenia

An abnormally low level of platelets in the blood. Platelets play a role in the blood clotting process.

Uncontrolled trial or study

A trial or study that does not have an intervention against which the intervention of interest is compared.

Urticaria

A disorder of the skin characterised by raised red, or red and white patches occurring in parts or over the whole body and attended by itching and irritation. It may be acute or chronic.

Utility

A measure of the strength of an individuals preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises all of the health-related qualities of life. Hence, utility has been described as a global measure of health-related quality of life.

Values

An alternative measure of the strength of an individuals preference for a given health state or outcome. In contrast to utilities, values reflect preferences without risk (or uncertainty).

1 AIM OF THE REVIEW

This review aims to address the effectiveness, cost-effectiveness and adverse effects of bupropion SR and nicotine replacement therapy (NRT) for smoking cessation. It does not address effects in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit.

2 BACKGROUND

2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

2.1.1 Problems associated with smoking

The health hazards of smoking are significant and well established. Diseases that are more common in smokers than in the general population include lung cancer, other lung disease, and cardiovascular disease.[1] Children and adolescents who smoke increase their risk for respiratory illness, are less physically fit, and may have blunted lung maturation compared with non-smoking peers.[2] Tobacco smoking is now the greatest single cause of illness and premature death in the United Kingdom, with more than 120 000 deaths of people aged over 35 years attributable to smoking. Furthermore, exposure to secondhand smoke by nonsmokers increases the risk for coronary heart disease. Infants are especially affected.[2] Environmental tobacco smoke has been linked with lung cancer in non-smokers.[1]

Smoking during pregnancy is one of the most important risk factors for neonatal and late foetal death.[1] Furthermore, women who smoke during pregnancy place the foetus at an increased risk of preterm delivery, low birth weight, miscarriage, and sudden infant death syndrome.[2] Parental smoking is estimated to be responsible for at least 17000 children under the age of five years being admitted to hospital in England and Wales each year.[1]

Cigarette smoke increases myocardial work and thereby oxygen demand, by increasing blood pressure, heart rate and cardiac output.[3] Also, coronary blood flow is reduced by coronary vasoconstriction and enhanced thrombosis. The carbon monoxide in cigarette smoke binds to haemoglobin thereby reducing the oxygen supply to the myocardium, and this could lead to a reduced level of exercise tolerance in patients with angina pectoris, intermittant claudication and chronic obstructive pulmonary disease (COPD).[3] Smoking is also associated with elevated blood viscosity, which is believed to contribute to platelet activation, which promotes atherogenesis. In addition, smokers have a higher risk lipid profile than non-smokers, which can be partly reversed within weeks of stopping smoking.[3]

Although nicotine is the amine alkaloid in tobacco smoke, it is primarily other smoke constituents that contribute to the adverse effects of tobacco use.[4] Besides nicotine, tobacco smoke contains about 4000 other components such as polycyclic aromatic hydrocarbons, aza arenes, N-notrosamine, aromatic amines, acrylonitrile, crotonaldehyde, vinyl chloride, formaldehyde, benzene and inorganic compounds.

From 1974 through to 1998 there was a substantial decline in the number of people smoking cigarettes from 51% to 41% respectively.[5] Unfortunately, the steady decline in the numbers of smokers observed in the 1970's and 1980's has levelled out since the 1990's. The latest UK General Household Survey in 1998 reports that at least 28% of all men and 26% of women aged 16 years or more smoke.[5] Between 1996 and 1998 the prevalence of smoking amongst men and women fell by 1% and 2% respectively.[5] Figures from 1998 also suggest that smoking is most prevalent amongst those aged 20-24 years old (42% for men and 39% for women) and lowest amongst men and women aged 60 years and over (16% for both men and women).[5]

2.1.2 Benefits of stopping smoking

Importantly, disease risks are reduced following smoking cessation, such that those smokers who stop before middle age can avoid most of the excess risk they would have carried.[1] The lipid profile and platelet reactivity improve following smoking cessation.[6] After only one year of abstinence the excess risk of myocardial infarction and cerebral arterial disease-related death are decreased by one half.[2] Smokers who stop before the age of 50 decrease their risk of dying from smoking-related causes by 50%. Depending on the number of years of abstinence, stopping smoking can reduce the risk of developing lung cancer by 20% to 90%.[7] The risk of developing oral cancer is cut in half after only three to five years and after ten years of abstinence the risk returns to that of a person who has never smoked.[7] In addition, stopping smoking normalises the decline in lung function found in patients with chronic obstructive pulmonary disease (COPD). Thus the benefits of stopping smoking are great.

2.1.3 Problems associated with giving up smoking

Unfortunately stopping smoking is not easy. Data from the latest UK General Household Survey in 1998[5] indicated that nearly 70% of smokers want to stop smoking completely. Similar data from the US 1994 National Health Interview Supplement[7] indicated that 46.4% of smokers had made a serious attempt to stop in the year prior to the survey, however, only

5.7% of smokers successfully abstained from smoking for a period of one month or more and only 2.5% of all smokers achieved permanent abstinence each year.

Smokers develop tolerance to some of the behavioural and sympthomimetic effects of nicotine over time, a process called neuroadaptation. When nicotine is stopped abruptly, withdrawal symptoms occur as a consequence of neuroadaptation.[8] Most withdrawal symptoms associated with tobacco dependence are significant and include the following: aggressiveness; anxiety; confusion; impatience; inability to concentrate; irritability; nicotine craving; restlessness; constipation; dizziness; headache; sweating[8] and difficulty sleeping.[9] Most withdrawal symptoms reach maximal intensity within 24 hours after cessation and diminish in intensity over two to four weeks. Some symptoms such as desire to smoke can persist for months or even years after cessation. In addition, whilst attempting to stop smoking there is the loss of perceived benefits of smoking, e.g. relief of stress[1], as well as concerns about weight gain.

2.1.4 Potential problems associated with the use of bupropion SR and NRT

Like all pharmacologically active agents NRT and bupropion SR have associated adverse effects. In the case of NRT the active pharmacological agent is nicotine, which smokers already self-administer. To further complicate matters, the adverse events associated with any smoking cessation intervention have to be differentiated from the unpleasant effects of stopping smoking i.e. withdrawal symptoms. Whether the adverse effects of NRT and bupropion SR are a significant deterrent to their use in smoking cessation, particularly in otherwise healthy people, will be addressed in this review.

2.2 CURRENT SERVICE PROVISION

2.2.1 NRT

The following NRTs are available in the United Kingdom.[10]

1. Nicotine transdermal patches
    - 5 mg, 10 mg, 15 mg (Nicorette® Pharmacia)
    - 0.7 mg/cm^2 (10cm^2, 20cm^2, 30cm^2) (Nicotinell® Novartis Consumer)
    - 7 mg, 14 mg, 21 mg (Niquitin CQ® SmithKline Beecham)

2. Nicotine Chewing gum
    - 2 mg, 4 mg (Nicorette® Pharmacia) (Nicotinell® Novartis Consumer)

3. Nicotine 2 mg sublingual tablet (Nicorette®Microtab Pharmacia)
4. Nicotine 1 mg lozenge (Nicotinell® Novartis Consumer Health)
5. Nicotine 2 mg and 4 mg lozenge (NiQuitin® SmithKline Beecham)
6. Nicotine 10 mg inhalation cartridge plus mouthpiece ((Nicorette®Inhalator Pharmacia)
7. Nicotine 0.5 mg per puff metered nasal spray (Nicorette® Pharmacia)

All products are licensed for use as an adjunct to smoking cessation and all are available either on general sale or on prescription through the National Health Service (NHS).[10]

2.2.2 Bupropion SR

In June 2000 the Medicines Control Agency granted a licence for bupropion hydrochloride sustained release (SR) (Zyban®GlaxoWellcome) as a prescription only drug to be used for smoking cessation (with motivational support) in the United Kingdom.[11] In the USA it is also indicated as an antidepressant and licensed as Wellbutrin®.

2.3 DESCRIPTION OF INTERVENTION

In this section the summary information presented is that provided by standard reference texts (MIMS,[10] BNF[12]).

Nicotine replacement therapy can assist smokers in abstaining from smoking by replacing some of the nicotine formerly obtained from tobacco.[8]

Dosage instructions vary according to the preparation of NRT being used. Transdermal patches have to be applied in the morning upon rising and removed either at bedtime or immediately prior to applying a new patch. They should be applied to non-hairy skin of the hip, chest (trunk) or upper arm. The initial dose should be of the highest strength (with some preparations this varies according to the number of cigarettes smoked per day), which should be used for three to four, six or eight weeks (according to preparation). All preparations recommend a gradual reduction in the strength of patch used before completing the course in approximately three months (10 to 13 weeks). With regard to the use of the highest strength NRT patch (Niquitin CQ®, 21 mg), patients are advised that if they experience excessive side-effects, which do not resolve in a few days, they should change to the 14 mg patch for the remainder of the initial phase of therapy.[12]

For the use of nicotine chewing gum, individuals who smoke 20 or fewer cigarettes per day are recommended to start with the 2 mg strength, and chew one piece of gum for about 30 minutes whenever the urge to smoke occurs. Individuals requiring more than 15 pieces of 2 mg strength gum per day may need the 4 mg strength gum (maximum intake 15 pieces per day).[10]

Nicotine lozenges are recommended when individuals feel an urge to smoke. The recommended dose is one 1 mg lozenge every 1-2 hours up to a maximum of 25 lozenges daily. Lozenge use should be withdrawn gradually after three months and the maximum period of treatment should be six months.[12]

With sublingual nicotine, individuals who smoke 20 cigarettes or less per day are recommended to take one 2 mg dose every hour. For those who fail to stop smoking or who experience significant withdrawal symptoms the 4 mg dose should be considered. Individuals who smoke more than 20 cigarettes per day are recommended to start on 4 mg per hour. The maximum recommended daily dose is 80 mg, with treatment continued for three months followed by a gradual withdrawal, giving an overall therapy period of six months.[10]

The nicotine inhalator is to be used whenever the urge to smoke arises. The initial dosage recommendation is for between six and 12 cartridges per day for up to eight weeks, followed by a reduction by half over the next two weeks and reducing to zero over the two weeks after that.[10]

The nicotine nasal spray is to be administered as needed up to a maximum of two puffs per hour for 16 hours per day. Treatment should continue for eight weeks and then be reduced gradually to zero over the next four weeks.[10]

The use of all NRT preparations is contraindicated in women who are pregnant or breast feeding.[10] In addition, Nicotinell® transdermal patches and chewing gum are contraindicated in acute MI, unstable angina, severe cardiac arrhythmias, recent stroke and skin disease.

Generally with NRT, special precautions are stipulated in people with severe cardiovascular disease (including severe arrhythmias, the immediate post-myocardial infarction period; or recent cerebrovascular accident including transient ischaemic attacks. In addition, the use of transdermal patch preparations of NRT are contraindicated in people with generalised skin disease (patches should not be placed on broken skin); nor should patches be used by occasional smokers.[12]

2.3.1 Bupropion SR

Bupropion SR is an atypical antidepressant drug. The mechanism by which it acts as an aid to smoking cessation is unclear, as is its mechanism of action as an antidepressant.[13] Bupropion SR is thought to produce its therapeutic antidepressant effects via inhibition of the neuronal uptake of noradrenaline and/or dopamine. In the UK bupropion SR is indicated as an aid to smoking cessation and is the only non-nicotine-based pharmacological agent licensed for this indication. Other non-nicotine-based agents that have been investigated as aids to smoking cessation include: mecamylamine, which is a nicotine antagonist;[14] other antidepressants (nortriptyline, doxepin, fluoxetine, and other serotonin reuptake inhibitors, and moclobemide);[15] clonidine; buspirone; sensory stimulants; silver acetate; opiod antagonists; corticotropin; and lobeline.[15, 16]

According to its product licence bupropion SR tablets 'are indicted as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients'.[17] Seizures have been reported with the use of bupropion SR. To minimise the risk of seizure with bupropion SR, the maximum daily dose should not exceed 300 mg and this should be administered in two equal doses.

The recommended dose of bupropion SR in smoking cessation has been amended very recently. The original recommendation of one tablet (150 mg) daily for *three* days increasing to two tablets daily allowing a minimum of eight hours between doses has been changed to one tablet (150 mg) for *six* days before commencing the higher dose. Treatment with bupropion SR should start whilst the patient is still smoking since it takes approximately seven days of treatment before bupropion blood levels achieve steady state.[17] Patients should set a target to stop smoking seven to 14 days after initiating treatment and should continue taking bupropion SR for seven to nine weeks.[10]

Bupropion SR is contra-indicated in patients with any of the following: hypersensitivity to bupropion or any of its excipients; current or previous seizure disorder; a current or previous diagnosis of bulimia or anorexia nervosa; patients with a known CNS tumour; abrupt withdrawal from alcohol or benzodiazepines; in patients with severe hepatic cirrhosis; in patients being treated with mono-amine oxidase inhibitors; and in patients with a history of bipolar disorder.

Bupropion SR must not be prescribed in patients with other risk factors for seizures unless there is compelling clinical justification for which the potential benefit of smoking cessation

outweighs the increased risk of seizure. In such patients a lower dose of 150 mg daily throughout the entire treatment period should be considered. Such risk factors include:

- Concomitant administration of any drug known to lower the seizure threshold (e.g antipsychotics, antidepressants, antimalarials, theophylline, systemic steroids, tramadol, quinolones and sedating antihistamines)
- Alcohol abuse
- History of head trauma
- Diabetes treated with hypoglycaemics or insulin
- Use of stimulants or anorectic products

If bupropion SR is used in combination with NRT, blood pressure should be monitored weekly.[10]

Due to its complex pharmacology bupropion SR has considerable potential for interaction with other medicines. Therefore, it is important to be aware of all medicines which patients are taking when considering their suitability for treatment with bupropion SR.

The most common adverse events reported to be associated with bupropion SR are insomnia and dry mouth. Adverse events which have been reported by more than 1% of patients are GI upset, abdominal pain, constipation, tremor, concentration disturbance, headache, dizziness, depression, agitation, anxiety, rash, pruritus, sweating, hypersensitivity type reactions, taste disorders. The incidence of seizures with bupropion SR has been reported to be 0.1%. Allergic reactions characterised by symptoms such as puritis, urticaria, angioedema, and dyspnoea have been reported, and there have been rare reports of erythema multiforme, Stephens-Johnson syndrome and analphylactic shock. Symptoms resembling serum sickness have also been reported.

Psychosis, confusion and other neuropsychiatric phenomena have been reported with bupropion, but primarily in depressed patients and not always with the sustained release formulation. No cases of activation of psychosis or mania have been reported in non-depressed patients treated with bupropion.

3 METHODS

The review consists of an overview of good quality systematic reviews evaluating the effectiveness of bupropion SR and/or NRT, which have been updated with newly identified,

randomised controlled trials (RCTs). A broader range of studies were considered for inclusion to establish the adverse events' profile of bupropion SR and NRT. In addition to RCTs, the types of studies considered for inclusion were non-randomised controlled studies, cohort studies, case-controlled studies, uncontrolled studies, surveys, surveillance data, case reports and case series. Relevant studies of economic evaluations have been reviewed and a new cost-effectiveness model has been developed.

3.1 SEARCH STRATEGY

A wide range of databases and other information resources were searched to locate details of both published and unpublished studies, and other information on the effectiveness, cost-effectiveness and safety of bupropion SR (Zyban®) and nicotine replacement therapy (NRT) for smoking cessation. A total of 25 electronic databases were searched, and searches of the World Wide Web were also undertaken. Full details are provided in Appendix 9.2.

The search strategies were devised by the Information Service Team at the NHS Centre for Reviews and Dissemination, University of York, and were checked by the review team.

Structure of the literature searches

To locate references on the effectiveness of bupropion SR and NRT in smoking cessation, literature searches initially focussed on identifying all relevant **systematic reviews** in the area.

A search strategy was then devised to identify any newly-published **randomised controlled trials** in order to update the references retrieved by previous systematic review searches.

For information relating to the **adverse effects and safety** of bupropion, literature searches were designed to retrieve studies of any design and systematic reviews wherever possible.

Searches on the **cost-effectiveness** of bupropion and NRT were conducted separately. No limits by study design were applied.

All initial searches were carried out between December and February 2001, and subsequently updated in April/May 2001. Resources were searched from their date of inception to the most recent date available at that time. There was no restriction of study by

country of origin, language or date of publication, although non-English language papers were not selected for inclusion in the review.

The bibliographies of retrieved references were scanned for further relevant publications.

References were managed using the EndNote4 software.

Search strategy

The core search strategy used for this review was as follows:

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
smok* or tobacco or nicotin*
#3 and #4
nicotine replacement therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7 or #8
#5 or #9

This strategy was designed for searching the MEDLINE electronic database (on SilverPlatter), and was adapted as appropriate for all other databases searched, taking into account differences in indexing terms and search syntax for each database. 'Buproprion' was used as a search term, as this appeared to be a commonly occurring spelling mistake.

The search strategy was subsequently modified to limit results by study type, to adverse effects/safety studies only, or cost-effectiveness studies only.

Full details of all databases searched and search strategies used are provided in Appendix 9.2. Information on database hosts and date ranges searched for each database is also included.

3.2 INCLUSION AND EXCLUSION CRITERIA

Two reviewers independently screened all titles and abstracts for relevance. Full paper manuscripts of any titles/abstracts which were of potential relevance, were obtained, and the relevance of each article assessed according to pre-defined criteria. Systematic reviews and other studies, which did not fulfil all of the criteria, were excluded and their bibliographic details listed, with the reason for exclusion (see Appendix 9.3). Any discrepancies were resolved by consensus and where necessary a third reviewer was consulted. Due to time constraints only references available in the English language have been included in the review. The inclusion criteria are detailed below:

3.2.1 Interventions

3.2.1.1 Clinical and cost effectiveness studies

Bupropion (150 mg/day, 300 mg/day), immediate (IR) and slow release (SR) formulations, used to aid smoking cessation alone; as part of combination therapy with motivational support; or as part of combination therapy with motivational support and NRT, were included.

NRT:

- Nicotine gum
- Nicotine transdermal patch
- Nicotine nasal spray
- Nicotine inhaler
- Nicotine sublingual tablet
- Nicotine lozenge

The main comparator was placebo, but other comparators eligible for inclusion were no treatment, other pharmacological agents, and non-pharmacological interventions such as accupuncture.

3.2.1.2 Adverse effects studies

As clinical experience with bupropion SR as an aid to smoking cessation is limited, bupropion IR and SR at any dose were considered. The protocol stated that data on the adverse effects of NRT would be restricted to those associated with doses of NRT appropriate to its use in smoking cessation. In practice, all doses of NRT were included.

3.2.2 Participants

3.2.2.1 Clinical and cost effectiveness studies

Participants were smokers of any age or gender. Where possible and appropriate, sub-groups have been identified.

3.2.2.2 Adverse effects

For adverse effects of bupropion SR, data related to any participants taking bupropion (IR or SR) for any indication have been considered for inclusion in the review. Advice received from a Consultant Psychiatrist indicated that the adverse events profile identified from a population of patients with depression was not likely to be significantly different from that in the general population and therefore, data from depressed patients have been included. The protocol stated that for the adverse effects of NRT only data pertaining to participants using NRT for smoking cessation would be eligible for inclusion. In practice all safety studies of NRT were included

3.2.3 Study design

3.2.3.1 Clinical effectiveness studies

The main data source for the evaluation of clinical effectiveness of both bupropion SR and NRT was good quality systematic reviews of RCTs. Where appropriate, the systematic reviews have been updated with information from newly identified RCTs. Only those systematic reviews meeting the inclusion criteria for the Database of Abstracts of Reviews of Effectiveness (DARE),[18] (Appendix 9.5) were considered further for inclusion in the review. As stated in section 3.2.4.1 below, only systematic reviews that included only studies with a minimum of six months follow-up or newly identified RCTs that met this criterion were included in this review.

3.2.3.2 Economic evaluations

Any relevant studies that evaluated cost-effectiveness or cost-utility of bupropion SR and/or NRT were eligible for inclusion, e.g. RCTs, prospective/retrospective cohort studies, and simulation modelling studies.

3.2.3.3 Adverse effects

For the evaluation of adverse events a broader range of studies, in addition to systematic reviews, were considered. These included non-randomised controlled studies, cohort

studies, case-controlled studies, uncontrolled studies, surveys, surveillance studies, case reports and case series. Studies were included if their primary objective was the investigation of the adverse effects, tolerability or safety of either bupropion (IR or SR) or NRT. Such studies were selected under the following specific categories:

- studies whose primary objective was to investigate the incidence of adverse events;
- investigations related to some specific aspect of the safety of the agent, e.g. effect on cardiovascular function;
- studies relating to use during pregnancy;
- case reports or case series relating to adverse events;
- surveillance studies.

3.2.4 Outcome measures

3.2.4.1 Clinical effectiveness studies

The main clinical outcome measure used was the number of participants who were not smoking at 6, 12, or more months after the start of therapy. Where possible, data from different durations of follow-up have been examined separately. Greater emphasis has been placed upon data derived from longer follow-up periods. Where possible continued abstinence rather than point prevalence has been used to report levels of smoking cessation. In several of the systematic reviews the 'best level of evidence' was used and so some results may include a combination of both continued and point abstinence. Smoking cessation should have been assessed by patient report and, ideally confirmed by breath test or another acceptable method.

3.2.4.2 Economic evaluations

For economic evaluations the outcome measures should be incremental cost per quitter, or per life year saved, or ideally, per quality adjusted life year saved (QALYs) compared with no or alternative interventions. Studies reporting cost-benefit of interventions for smoking cessation have also been included.

Studies reporting cost per QALYS are necessary to compare bupropion SR or NRT treatment with other health care technologies. Studies reporting cost per quitter may be sufficient to compare between different interventions for smoking cessation, including bupropion SR, NRT, brief advice, self-help material, etc. (if adverse effects are not significantly different across different interventions).

3.2.4.3 Adverse effects

The incidence and severity of all adverse events have been reviewed.

3.3 DATA EXTRACTION STRATEGY

All relevant data including study details, study quality, details of participants, interventions and results have been extracted by one reviewer into an ACCESS database, and independently checked for accuracy by a second reviewer (example extraction sheets shown in Appendix 4). Data from studies with multiple publications were extracted and reported as a single study. The data-extraction sheet for identified studies of economic evaluation is in Appendix 9.4.

3.4 QUALITY ASSESSMENT STRATEGY

The quality of systematic reviews and studies meeting the inclusion criteria have been assessed by one reviewer and independently checked by another reviewer. Disagreements were resolved through consensus and if necessary a third reviewer has been consulted.

The quality of systematic reviews of effectiveness and/or side effects have been assessed using criteria developed for the Database of Abstracts of Reviews of Effectiveness (DARE) (see Appendix 9.5).[18]

The quality of RCTs have been assessed using criteria based on CRD Report No. 4 (See Appendix 9.5).[19] The quality of primary studies, from which adverse event data were extracted, were assessed according to checklists based on standard critical appraisal checklists as appropriate (see Appendix 9.5).[20] In the process of the review a number of uncontrolled studies of various types were identified (e.g small uncontrolled acute studies, large pooling of data from clinical trials). It was decided that the checklist for a cohort study was applicable both to studies that were cohort studies in the strict sense of the term (i.e, investigations in which a group of individuals (the cohort) is identified and followed prospectively, perhaps for many years, and their subsequent medical history recorded, in which, the cohort may be subdivided at the onset into groups with different characteristics, for example, exposed and not exposed to some risk factor, and at some later stage a comparison made of the incidence of a particular disease in each group) and to studies that merely investigated a cohort of patients in a more general sense. Initially in preparing this report all these types of studies were referred to as ‘cohort studies’, however, to avoid confusion between very different study types the more general use of the term ‘cohort’ has

been abandoned and replaced with the term 'uncontrolled'. The term 'cohort study' is now used only in its stricter sense. Although some studies have been reclassified from 'cohort' to 'uncontrolled' in the dcourse of this review, the quality assment using the cohort study checklist is still appropriate.

This information has been presented in table form and summarised within the text of the report.

The protocol stated that criteria based on the Drummond checklist would be used to assess the quality of economic evaluations (See Appendix 9.5),[21] however, this was not done due to their limited utility and time constraints. In this review, the economic evaluation of NRT and bupropion SR for smoking cessation has focused on the development of a decision analysis model.

3.5 METHODS OF ANALYSIS/SYNTHESIS

3.5.1 Clinical effectiveness studies

Details of the extracted data and quality assessment for each individual systematic review and RCT of effectiveness are presented in structured tables and as a narrative description. The possible effects of study quality on the effectiveness data are discussed. The pooled estimates from included systematic reviews, updated with data from newly identified RCTs are presented. Where possible, subgroup analyses have been conducted to assess differences in effectiveness between different participant groups.

3.5.2 Economic evaluations

Included studies of economic evaluation of bupropion SR and/or NRT are grouped according to type of evaluation (CE, CU, CB); type of outcomes; type of comparators; and country of origin. Economic evaluation studies conducted in the UK with an NHS perspective have been particularly emphasised.

Based on new evidence of the effectiveness of bupropion SR and/or NRT, a model has been developed to estimate cost per life-year saved and per quality-adjusted life-years saved. The number of life-years saved and the quality-adjusted life-years saved have to be estimated by modelling and based on the number of quitters. Ideally, estimation of quality of life-years should consider any adverse effects resulting from smoking cessation interventions and comparators.

Two commonly used approaches for estimating life-years saved from number of quitters are (1) use of an established computer model PREVENT, or (2) a comparison of mortality between smokers and ex-smokers or non-smokers based on data from health surveys. These approaches have been assessed based on the existing literature and their outcomes compared in the review.

Costs of smoking cessation interventions may include costs to providers of smoking cessation interventions, costs (and savings) to patients and families, to other care agencies, and to employers. In this review, modelling of cost-effectiveness is from the perspective of the National Health Service. Thus the costs of smoking cessation interventions will be the costs to the NHS, including costs of health professionals' time, costs of NRT or bupropion SR, and costs of patient education material. Costs to the NHS may be separated into short-term costs related to the smoking cessation interventions and long-term costs of health care for smokers who stop smoking. It is relatively straightforward to measure the direct costs of a programme but very complicated to measure its impact on long-term health care spending.[22] In this review, research about the impact of smoking cessation interventions on health care spending, each linked to outcomes (QALYs and quitters) has been summarised, but the modelling has focused on the short-term direct costs of smoking cessation programme.

To estimate the potential gains in population health and the cost impact on the NHS, the prevalence of smokers, the proportion of smokers who are motivated to quit, and of usage of bupropion SR, NRTs and other smoking cessation interventions needs to be estimated. For example, in the model of Parrott et al 1998, it was estimated that 50% of current smokers would be advised to stop, 40% of smokers who received advice would attempt to quit, and 30% of smokers who attempt to quit would use NRTs.[22] In another model, the Health and Economic Consequences of Smoking Model (HECOS), the default proportion of usage of different interventions for smoking cessation in the UK is 25% for pharmacological therapy, 10% for gP advice, 2% for group session, and 63% for willpower (no intervention) (http://www.ea3.lewin.com/hecos/whoweb.asp). The estimates and assumptions about the proportions of smokers who attempt to quit and usage of different interventions in the literature have been assessed, and updated where new or more reliable data were available.

Any long-term costs and benefits following smoking cessation are discounted according to recommended UK Treasury rates, that is, costs at 6% per annum and long-term health benefits at 1.5% per annum. Sensitivity analyses have been conducted to explore the impact of uncertainty in estimating incremental cost and effectiveness, and the choice of different rates of discounting.

3.5.3 Adverse effects

The incidences of adverse events are summarised by intervention and for comparators where appropriate.

4 RESULTS

A total of 1551 references were identified from the literature searches. For effectiveness and safety a total of 451 references were ordered and checked for inclusion in the review. Of these a total of 135 references were included in the review and 316 references were excluded. All excluded references are listed in Appendix 9.3, with their reason for exclusion. In addition three company submissions were received. A total 17 references relevant to the economic evaluation of bupropion SR and NRT in smoking cessation were identified from the literature searches and assessed.

4.1 CLINICAL EFFECTIVENESS

4.1.1 Nicotine replacement therapy (NRT)

Two systematic reviews,[23, 24] five newly identified published RCTs[25-29] and two unpublished RCTs (commercial in confidence) [30, 31] met the criteria for inclusion in the review.

4.1.1.1 Systematic reviews

Description of systematic reviews

Of the two systematic reviews, one[24] was conducted by the Cochrane Tobacco Addiction Review group, and the other[23] is a US Public Health Service report. The US report includes only articles published in peer reviewed journals between 1 Jan 1975 and 1 Jan 1999 and, therefore, is less comprehensive and less up to date than the Cochrane Review. Therefore, only the NRT data from the Cochrane Review has been used in this report.[24]

Only RCTs of smokers of either gender, irrespective of setting and/ or initial level of nicotine dependency, which reported an outcome of smoking cessation and had a follow-up of at least six months, were included in the Cochrane Review.[24] In each study the strictest available definition of abstinence was used and wherever possible, continued abstinence rate rather than point prevalence was used. In trials where participants were lost to follow-up they were regarded as being continuing smokers. Only studies that compared NRT with

placebo or no treatment were included, with the exception of those that compared different doses of NRT. Data from one comparison of NRT with bupropion SR were also included.

The Cochrane Review also determined the effectiveness of NRT in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit. This is not an objective of the present review and therefore, these data have not been discussed further.

One hundred and eight RCTs and quasi-RCTs were included in the Cochrane Review (see Appendix 9.12 for full reference list). Of these, 36 studies were true RCTs (i.e. they reported randomisation procedures in sufficient detail for it to be clear that selection bias was minimised), five were quasi-RCTs (they randomised to treatment according to day of week or clinic attendance) and 67 were RCTs that, either did not report how randomisation was performed, or reported it in insufficient detail to determine whether a satisfactory attempt to control selection bias had been made. The quality of bias control did not differ significantly between trials of different forms of NRT. Three trials were included based on data available from abstracts.

Specific interventions included in the Cochrane Review were: nicotine chewing gum (2 mg or 4 mg or both or variable) for 3 weeks to 12 months; nicotine transdermal patches 16 or 24 hour patches (doses not specified, but some studies compared patches of different strengths) for a minimum of 6 weeks to 3 months, with a tapering period in some trials; nicotine nasal spray (details not given); nicotine inhalers/inhalators (details not given); and nicotine tablets (details not given). [24]

Studies included in the Cochrane Review varied considerably in terms of the definitions of abstinence used. Twenty-seven of the trials reported the primary long-term outcome as point prevalence abstinence, 75 as continued abstinence, and five failed to specify the approach used. One remaining study looked at a reduction in smoking rather than abstinence. All but 11 of the trials used some form of validation of self-reported smoking cessation. Validation of the abstinence was carried out by blinded methods (measurements of metabolites in body fluids) in 21 trials. Measurement of carbon monoxide in expired air was the most common form of validation used. However, the 'cut-off' level of carbon monoxide used to define abstinence varied from less than 4 to 11 parts per million (ppm). In one trial, participants who smoked up to three cigarettes per week were still classified as abstinent.

With the exception of 12 gum trials and 13 patch trials, participants were followed for at least 12 months.

Twenty-two of the studies included in the Cochrane Review were conducted in primary care. Five were in workplace settings, two in a university clinic and one in a Veteran's Affairs (VA) Medical Centre. Eight studies were in specialised smoking-cessation clinics and seven trials were in hospitals (usually patients with smoking-related illness). Three studies were of "over the counter" NRT. The remaining trials were in community settings, where participants had been recruited in response to media advertisements and were treated in smoking cessation clinics.

All trials included both male and female participants except for two: one (included only in comparison of 4 mg with 2 mg gum) included only males and another NRT gum study included only females. One study included only relapsed smokers.

Quality of systematic reviews

This assessment is presented in full in Appendix 9.8.7. The Cochrane Review was a good quality systematic review.[24] The searches conducted for the review were comprehensive for both published and unpublished literature. The inclusion criteria for study design, participants, intervention and outcomes all related to the purpose of the review and were applied independently by two authors. The validity of the studies was checked formally according to specified criteria and were applied independently by two authors. Validity was not really taken into account in the review. Data extraction was performed independently by more than one author and individual study details are presented in the review. Appropriate meta-analyses with tests for heterogeneity have been performed and the results presented in full.

4.1.1.2 Newly identified RCTs

Description of newly identified RCTs

Five newly identified published RCTs of NRT were included.[25-29] One was a study of NRT patches in pregnant women,[29] one was a comparison of NRT patch plus telephone support with NRT patch alone[28] and the other three were comparisons of NRT with another active treatment. (It should be noted that one of these three studies[27] was included in the Cochrane review[24], but only as a comparison with placebo, and not the comparison with an active intervention included here.) In addition two unpublished studies were identified.[30, 31] One was a placebo-controlled comparison of 2 mg and 4 mg dose NRT lozenge and one was a comparison of NRT gum (4 mg) with bupropion SR. Limited details of these unpublished studies are presented in Appendix 9.6.1. Further details are omitted from this report for reasons of commercial confidentiality.

Quality of newly identified RCTs

These data are presented in full in Appendix 9.8.1. None of the five published trials fully reported the randomisation procedure. Three of the trials were reported to be double-blind, [26, 27, 29, 32] but one study was not blinded between the two treatments of interest (NRT and naltrexone).[27] The other two studies were unblinded[25, 28] Concealment of allocation was judged to be adequate in two trials[27 29] and unclear in two.[26 28] Only one study reported using a power calculation *a priori* for sample size.[26] All of the studies reported participant eligibility criteria. All studies reported comparable groups at baseline, although five participants did not appear to be included in the demographic summary in one trial.[25] One trial provided weekly or biweekly 15-20 minute counselling sessions for both study groups throughout the treatment period,[27] one study[29] included four clinic visits or telephone calls and one study[28] included telephone support in one treatment arm only. All of the studies reported the statistical methods used, but only one reported the degree of variability around the point estimates.[26] All studies undertook intention to treat (ITT) analyses although in one study withdrawals were not clearly reported.[25] Adherence to the study protocol was not explicitly reported in any study, although use of active and placebo patches was reported as low in the study in pregnant women.[29] The definition of abstinence varied. Two studies relied on self-reports and measured carbon monoxide (CO) levels.[26, 28] One trial used daily diary records, with confirmation with CO measurements at every assessment (no more than 8 parts per million (ppm) and CO level less than 9ppm).[27] Another trial used CO levels less than 4ppm.[25] The study in pregnant women[29] used self report and saliva cotinine levels.

4.1.1.3 Clinical effectiveness results from systematic reviews and newly identified RCTs of NRT therapy

All the results presented in this section are those derived from systematic reviews which have been updated with newly identified RCTs where available.

The effectiveness of NRT versus placebo or no intervention

The results for the effects of NRT on smoking cessation (rate of abstinence from smoking achieved) compared with those for placebo or no intervention are summarised in Table 1 and presented graphically in Appendix 9.11. These are derived from the Cochrane review.[24] The two newly identified unpublished RCTs[30] [29] that could have updated this review are unpublished and have therefore not been included.

Table 1. Abstinence from smoking in smokers followed for at least six months (longest duration of follow-up available): rates and pooled odds ratios (published data only)

Comparison	Abstinence rates on treatment	Abstinence rates on placebo or no treatment	Peto OR (95% CI)	P value for comparison	Number of studies in meta-analysis	Chi square test for heterogeneity (df) (p value)
NRT gum	1508/7674	1110/9613	1.66 (1.52, 1.810	P <0.00001	51	60.70 (50) (p=0.14)
NRT patch	1438/10019	526/6285	1.74 (1.57, 1.93)	P<0.00001	35	47.48 (34) (p=0.06)
NRT inhaler	84/490	44/486	2.08 (1.43 to 3.04)	P = 0.0001	4	1.34 (3)(p=0.72)
NRT nasal spray	107/448	52/439	2.27 (1.61 to 3.20)	P<0.00001	4	1.22, (3)(p = 0.75);
NRT sublingual tablet/lozenge	49/243	31/245	1.73 (1.07, 2.80)	P=0.02	2	0.10 (1) (0.75)
Any NRT	3166/18874	1763/17068	1.72 (1.61, 1.84)	P<0.00001	96	115.06 (95) (p=0.08)

If the results are pooled using a random effects model the odds ratio for any NRT is 1.77 (95% CI: 1.63, 1.91).

Although the specific details of the unpublished trials cannot be presented in this report for reasons of commercial confidentiality, this restriction does not apply to an overall summary of the data. If the two unpublished studies are included the result for any NRT is Peto OR 1.74 (95% CI: 1.64, 1.86) or using a random effects model, OR 1.79 (95% CI: 1.65, 1.93).

Table 2 includes only the published studies reporting data for the proportion of participants achieving 12 months' or more continued abstinence. These data are presented graphically in Appendix 9.11.

Table 2. Abstinence from smoking in smokers followed for at least 12 months: rates and pooled odds ratios (published data only)

Comparison	Abstinence rates on treatment	Abstinence rates on placebo or no treatment	Peto OR (95% CI)	P value for comparison	Number of studies in meta-analysis	Chi square test for heterogeneity (df) (p value)
NRT gum	1109/6187	861/7788	1.61 (1.45 to 1.78)	p<0.00001	38	49.44 (37) (0.08)
NRT patch	917/6812	363/4156	1.62 (1.42 to 1.84)	p<0.00001	23	34.30 (22) (0.05)
NRT inhaler	84/490	44/486	2.08 (1.43 to 3.04)	p = 0.0001	4	1.34 (3) (0.72)
NRT nasal spray	107/448	52/439	2.27 (1.61 to 3.20)	p<0.00001	4	1.22 (3) (0.75)
NRT sublingual tablet/lozenge	49/243	31/245	1.73 (1.07 to 2.80)	p = 0.02	2	0.10 (1) (0.75)
Any NRT	2266/14181	1351/13114	1.66 (1.54 to 1.79)	p<0.00001;	71	91.53 (70) (0.04)

If the results are pooled using a random effects model the OR for any NRT is 1.71 (95% CI: 1.55, 1.88).

Although the specific details of the unpublished trials cannot be presented in this report for reasons of commercial confidentiality, this restriction does not apply to an overall summary of the data. If the unpublished study is included the result for any NRT is Peto OR 1.69 (95% CI: 1.57, 1.82) or using a random effects model, OR 1.74 (95% CI: 1.58, 1.91).

The results for abstinence at 12 months or longer are not greatly altered from when the shorter-term data are included. There is an indication of heterogeneity in the analyses for any

NRT. This heterogeneity stems from the heterogeneity within the patch studies and the gum studies. The inclusion criteria for the review from which these analyses are derived were very general. The inclusion of such a clinically diverse range of studies does, however, increase the generalisability of the findings. The forest plots of the meta-analyses would suggest that the pooling of these heterogenous patch studies and gum studies may result in an underestimate of the overall beneficial effect of NRT.

The effectiveness of NRT versus placebo in subgroups

The effectiveness of NRT versus placebo has been studied in the following sub-groups: smokers with lung disease; smokers with cardiovascular disease; smokers with pulmonary or vascular disease; smokers with smoking related diseases (not specified); and pregnant women smokers. These data are presented graphically in Appendix 9.11.

a) Smokers with lung disease

Two studies were included in this analysis.[33] [34] For details of these studies the reader is referred to the Cochrane review.[24] The pooled abstinence rates were 18/134 with NRT compared with 5/141 with placebo, giving a Peto OR of 3.84 (95% CI: 1.61, 9.15; p=0.002). These data are presented graphically in Appendix 9.11.

b) Smokers with cardiovascular disease

There was only one study that included only smokers with cardiovascular disease in the analysis.[35] For details of this study the reader is referred to the Cochrane review.[24] The abstinence rates were 29/294 with NRT compared with 35/290 with placebo, giving a Peto OR of 0.80 (95% CI: 0.48, 1.34; p=0.4).

c) Smokers with pulmonary or vascular disease

There was only one study that included only smokers with pulmonary or vascular disease (mixed population) included in the analysis.[36] For details of this study the reader is referred to the Cochrane review.[24] The abstinence rates were 39/410 with NRT compared with 111/1208 with placebo, giving a Peto OR of 1.04 (95% CI: 0.71, 1.53; p=0.08).

d) Smokers with smoking related diseases (not specified)

Two studies were included in this analysis [37, 38] For details of these studies the reader is referred to the Cochrane review.[24] The pooled abstinence rates were 51/285 with NRT compared with 43/291 with placebo, giving a Peto OR of 1.25 (95%CI: 0.80, 1.94; p=0.3).

e) Pregnant women smokers

One study investigated the effectiveness of NRT versus placebo in pregnant women smokers.[29] Details of this study are given in Appendix 9.6.1. At the fourth pre-natal visit (scheduled for four weeks prior to the expected delivery date) 28% of the NRT group were abstinent compared with 25% of the placebo group. It should be noted that compliance with NRT patch use was poor, with only 17% of participants in the NRT group and 8% in the placebo group using all the 15 mg patches and 11% and 7% respectively using all 10 mg patches. At 12 months post-partum 15% of the NRT group and 14% of the placebo group were abstinent, giving a Peto OR of 1.09 (95% CI: 0.54, 2.18).

Other comparisons

Other comparisons were made within the Cochrane review.[24] These are summarised below and presented graphically in Appendix 9.11. A comparison of 4 mg versus 2 mg gum in high dependency smokers (i.e. smokers highly dependant on nicotine, usually having a Fagerstrom score of 7 or more) included four trials, giving an OR of 2.18 (95% CI: 1.49, 3.17; p = 0.00005; test for heterogeneity chi-squared = 4.07, df = 3, p = 0.25). Also, high dose nicotine patches were compared with low dose patches in six trials. Data pooled from three trials which compared 44 mg patches with 22 mg patches gave an OR of 1.18 (95% CI: 0.90, 1.55; p = 0.2; test for heterogeneity chi-squared = 4.65, df = 2, p = 0.098). Three trials which compared 25 mg patches with 15 mg patches produced an OR of 1.22 (95% CI: 1.00, 1.49; p = 0.05; test for heterogeneity chi-squared = 1.28, df = 2, p = 0.53). The results were dominated by the inclusion of one large trial.

The Cochrane Review[24] found that only one trial made a direct comparison between NRT patches designed for wearing for different durations (i.e. 16 hours or 24 hours) before applying a new patch. This study gave an OR of 0.62 (95% CI: 0.26, 1.47; p = 0.3). Pooled results from nine trials where 16 hour nicotine patches were used gave an OR of 1.80 (95% CI: 1.51, 2.15; p<0.00001; test for heterogeneity chi-squared = 20.23, df = 8, p = 0.0095), however, there was significant heterogeneity between the studies. Pooled data from 26 trials which used 24 hour nicotine patches produced an OR of 1.76 (95% CI: 1.55, 2.00; p<0.00001; test for heterogeneity chi-squared = 27.73, df = 25, p = 0.32).

The effect of duration of NRT therapy has only been compared directly in two RCTs. One study compared 28 weeks duration of therapy with 12 weeks (OR 1.06 (95% CI: 0.86, 1.31; p = 0.6)) and the other compared 12 weeks duration of therapy with 3 weeks (OR=0.51, 95% CI: 0.20, 1.49; p = 0.2)). Pooling of ten studies with less than 8 weeks of therapy gave an OR of 2.30 (95% CI: 1.81, 2.92; p<0.00001; test for heterogeneity chi-squared = 6.15, df = 9, p = 0.73). Pooled data from 23 studies with longer than 8 weeks duration of therapy gave an

OR of 1.72 (95% CI: 1.51, 1.96; p<0.00001; test for heterogeneity chi-squared = 32.00, df = 22, p = 0.077).

Two studies investigated the effects of a fixed schedule of nicotine gum compared with an ad libitum schedule. The OR was 1.29 (95% CI: 0.90, 1.84; p = 0.17; test for heterogeneity chi-squared = 0.47, df = 1, p = 0.49). These results were dominated by one large study.

Two studies directly compared abrupt withdrawal of nicotine patches with weaning, giving an OR of 0.98 (95% CI: 0.59, 1.63; p = 0.9; test for heterogeneity chi-squared = 0.05, df = 1, p = 0.83).

The effects of different levels of motivational support given to patients on the effectiveness of NRT was also examined in the Cochrane Review.[24] Low intensity support was defined as part of the provision of routine care in the Cochrane Review.[24] High intensity support was defined as any support that involved at least 30 minutes duration at the initial consultation, or more than two further assessments or consultation visits.

Pooled results from 33 trials where participants received low intensity support in addition to NRT produced an OR of 1.75 (95% CI: 1.57, 1.96; p<0.00001; test for heterogeneity chi-squared = 47.40, df = 32, p = 0.039). The pooled ORs for gum plus low intensity support and patch plus low intensity support were 1.76 (95% CI: 1.52, 2.04; p<0.00001; test for heterogeneity chi-squared = 28.70, df = 20, p= 0.094) and 1.74 (95% CI: 1.48, 2.05; p<0.00001; test for heterogeneity chi-squared = 18.68, df = 11, p = 0.067), respectively.

Pooled results from 49 studies of high intensity support in addition to NRT compared with NRT alone, gave an OR of 1.68 (95% CI: 1.53, 1.84; p<0.00001; test for heterogeneity chi-squared = 53.02, df = 48, p = 0.29). The pooled ORs for gum plus high intensity support and patch plus high intensity support were 1.59 (95% CI: 1.40, 1.80; p<0.00001; test for heterogeneity chi-squared = 25.50, df = 26, p = 0.49) and 1.78 (95% CI: 1.56, 2.03; p<0.00001; test for heterogeneity chi-squared = 26.08, df = 21, p = 0.2) respectively.

It is stated in the Cochrane review[24] that three studies directly compared the effect of high-intensity versus low-intensity support (two studies with gum, and one with patch). This direct comparison was not included in the Cochrane review and is, therefore, not available for the present review.

One newly identified RCT[28] investigated the effectiveness of supplementing free NRT patches with motivational support. The motivational support consisted of proactive telephone

support, approximately biweekly for a period of three months. The participants included in the study were 214 female smokers, recruited through media advertisements and communicated with by mail and telephone. Further details of the study are given in Appendix 9.6. At 6-months follow-up the abstinence rates were 24/106 (23%) in the NRT patch plus support group compared with 20/108 (19%) in the patch alone group, giving an odds ratio of 1.29 (95% CI: 0.66, 2.49).

The effect of clinical/recruitment setting was not directly compared in any of the included studies. The pooled results for different settings by type of NRT (patch or gum) are presented in Table 3.

Table 3. The effect of clinical/recruitment setting on effectiveness of NRT versus placebo or no treatment

Type of NRT	Setting	Peto OR (95% CI)	P value for comparison	Number of studies in meta-analysis	Chi square test for heterogeneity (df) (p value)
NRT gum	Community	1.67 (1.46 to 1.90)	p<0.00001	24	33.54 (23) (0.072)
	Smoking clinic	1.98 (1.56 to 2.52)	p<0.00001	7	5.81 (6) (0.45)
	Primary Care	1.76 (1.50 to 2.07)	p<0.00001	18	13.80 (17) (0.68)
	Hospital	1.13 (0.84 to 1.51)	p=0.4	3	1.28 (2) (0.53)
NRT patch	Community	1.92 (1.67 to 2.22)	p<0.00001	20	28.33 (19) (0.077)
	Primary care	1.47 (1.18 to 1.83)	p=0.0005	6	8.38 (5) (0.14)
	Hospital*	1.74 (1.19 to 2.54)	p=0.004	4	2.09 (3) (0.55)
	OTC **	1.96 (1.41 to 2.72)	p=0.00007	3	0.54 (2) (0.77)

**Hospital denotes hospital inpatients or hospital outpatients. It does not refer to smokers attending smoking clinics based in hospitals nor to mixed populations of hospital patients and community volunteers*

***OTC over-the-counter*

The results are presented graphically in Appendix 9.11.

The evidence for the effectiveness of NRT in aiding smoking cessation in hospital inpatients or outpatients is weaker than that for participants treated in primary care or community volunteers. Attempts at smoking cessation with the aid of NRT appear to be somewhat less successful when conducted in the hospital setting, although whether this relates to the setting or to the nature of the participants, or as is likely, a combination, cannot be concluded from the evidence.

Summary of findings of NRT versus placebo or no intervention

These data demonstrate the effectiveness of NRT compared with placebo or no treatment in smoking cessation. This summary of the data also highlights the fact that the majority of NRT studies have been performed using either the gum or patch. There is clear evidence of

statistical heterogeneity within the gum and within the patch studies, which reduces the reliability of the pooled estimate of effect. The effect of this heterogeneity is likely to result in an underestimation of the effect of NRT.

Analyses of the effectiveness of NRT versus placebo or no intervention in sub-group populations is based on only a small number of trials. Evidence based on two studies in smokers with lung disease and in two studies of patients with smoking related diseases indicate that NRT is as effective in these sub-groups as in the general smoking population. In the other subgroups investigated, evidence from a single study in each case suggests no benefit of NRT over placebo. The weakness of this evidence must be borne in mind when interpreting these sub-group analyses.

The analyses indicate that high-dependency smokers can benefit from the use of higher doses of NRT gum. The results of the low-dose, high-dose NRT patch comparisons are equivocal.

The data suggest there is no real difference between the effectiveness of the 16 hour or 24 hour patch. Any differences between them will be related to adverse reactions, clinical need and personal preference.

Overall, the data suggest that even short-term therapy with NRT is more effective that placebo, but no real conclusions can be drawn regarding the relative effectiveness of different durations of therapy.

There appears to be no clear benefit in terms of effectiveness for fixed schedule versus *ad libitum* dosing or gradually weaning participants off NRT therapy rather than stopping therapy abruptly. Further studies may resolve these questions.

No firm conclusions can be drawn from the indirect comparison of high and low intensity support. High-level support does appear to result in higher absolute levels of abstinence and the differential between NRT and placebo is maintained. Evidence from one direct comparison of NRT patch, with and without support is not unequivocally in favour of additional support.

The evidence for the effectiveness of NRT in aiding smoking cessation in hospital inpatients or outpatients is weaker than that for participants treated in primary care or community volunteers.

Comparison of NRT versus other interventions for smoking cessation

a) NRT versus other NRT or combinations of NRT

Several studies explored the effect of comparing different combinations of NRT with NRT alone and were pooled within the Cochrane review.[24] The data are presented graphically in Appendix 9.11. The pooled OR for combination NRT versus monotherapy NRT was 1.55 (95% CI: 1.17, 2.05; p = 0.002; test for heterogeneity chi-squared = 7.93, df = 4, p = 0.094). Three of the individual studies showed a positive treatment effect for combined NRT over monotherapy NRT. These studies compared NRT patch plus gum with patch alone, patch plus gum with gum alone, and patch plus inhaler with inhaler alone. Only nasal spray plus patch versus patch alone reached statistical significance (OR=2.85, 95% CI: 1.49, 5.45; p=0.002). One study (patch plus inhaler versus either patch or inhaler alone) found a non-significant difference in favour of single NRT therapy (OR=0.59, 95% CI: 0.20, 1.43; p = 0.2).

Summary of findings of NRT versus other NRT or combinations of NRT

There is some indication that NRT combination therapy is more effective than NRT monotherapy. Whether or not the effectiveness of combination NRT is mainly due to the resulting increased dose of NRT needs further investigation. Further information is also required about the type of participants concerned, particularly with regard to their level of nicotine dependence.

b) NRT versus bupropion SR

One study comparing NRT directly with bupropion SR[39] was incorporated in the Cochrane Review.[24] This was a double-blind, double-dummy comparison of NRT patch with bupropion SR. A second, as yet unpublished trial was an unblinded comparison of NRT gum (4 mg) with bupropion SR.[31] It should be noted that these two studies are also discussed in the section on effectiveness of bupropion.

These studies have not been pooled as there is significant clinical heterogeneity. Table 4 presents the analysis from the Cochrane Review, which is based on the single double-blind study mentioned above.[39]

Table 4. Comparison between NRT patch and bupropion SR

Comparison	Proportion of abstainers in first group	Proportion of abstainers in second group	Odds ratio (95% CI fixed effect model)
Bupropion SR versus NRT patch	45/244	24/244	2.07 (1.22, 3.53)
Bupropion SR plus patch versus NRT patch	55/245	24/244	2.65 (1.58, 4.45)
Bupropion SR plus patch versus bupropion SR alone	55/245	45/244	1.28 (0.82, 1.99)

The ORs favour bupropion SR, suggesting that bupropion SR is more effective than NRT and that the effectiveness is not enhanced by its combination with NRT. These findings should be treated with some degree of caution as they are based on a single RCT.

Summary of findings for NRT versus bupropion SR

The available data suggest that bupropion SR may be more effective than NRT patch but that overall, no firm conclusions can be drawn regarding the relative efficacy of NRT compared with bupropion SR in smoking cessation.

c) NRT versus other active interventions

The Cochrane Review of NRT in smoking cessation did not include direct comparisons of NRT with other active interventions.[24] Three newly identified published RCTs have been identified that compared NRT with a comparator other than placebo or no treatment.[26] [25] [27] Details of these studies are given in Appendix 9.6.1.

RCT by Wong and colleagues[27]

This placebo-controlled study that compared NRT patch with naltrexone (a long-acting opoid antagonist which blocks certain effects of drugs such as heroin and morphine) found that continued abstinence at six months was achieved in 28% of participants receiving NRT patch, in 9% of participants receiving naltrexone only, in 27% of participants receiving patch plus naltrexone, and in 8% with placebo alone. The Peto OR for NRT patch versus naltrexone was 3.50 (95% CI: 1.72, 7.14; p=0.0006)

RCT by Clavel-Chapelon and colleagues[26]

This placebo-controlled trial compared nicotine gum 2 mg (ad libitum) with acupuncture and their combination. Abstinence rates at the 12-month assessment were as follows: placebo gum plus placebo acupuncture, 10.3% (95% CI: 7.1, 14.7); placebo gum plus acupuncture, 6.5% (95% CI: 4.1, 10.1); nicotine gum plus placebo acupuncture, 10.9% (95% CI: 7.4, 15.9) and; nicotine gum plus acupuncture, 11.2% (95% CI: 8.0, 15.5). There was no statistically significant difference (Log rank test) between the treatments. The Peto OR calculated for NRT versus acupuncture is 1.71 (95% CI: 0.90, 3.26; p=0.1)

At a 4-year assessment, abstinence rates were: placebo gum plus placebo acupuncture, 7.3% (95% CI: 4.5, 11.6); placebo gum plus acupuncture, 5.1% (95% CI: 3.0, 8.5); nicotine gum plus placebo acupuncture, 6.2% (95% CI: 3.2, 11.8) and; nicotine gum plus acupuncture, 6.1% (95% CI: 3.7, 9.9). There was no statistically significant difference (Log rank test) between the treatments. The Peto OR calculated for NRT versus acupuncture was 1.23 (95% CI: 0.84, 1.80; p=0.3)

RCT by Jensen and colleagues [25]

This study compared silver acetate chewing gum with NRT gum and ordinary gum. Abstinence rates at the 6 months' assessment was as follows: nicotine chewing gum, 42.6% (n=90); silver acetate, 38.9% (n=79) and; ordinary chewing gum, 34.2% (n=28). There was no statistically significant difference between treatments for percentage abstinence at 6-months. Peto OR calculated for NRT gum versus silver acetate was 0.75 (95% CI: 0.51, 1.11; p=0.3)

Summary of findings of NRT versus other active interventions

The comparison between NRT patch and naltrexone indicates that NRT is more effective that naltrexone in smoking cessation. The other two comparisons of active interventions both failed to find any difference between NRT and the other active intervention, and both failed to find NRT to be statistically significantly better than placebo. In one study the response to all interventions was low,[26] whilst in the other study the placebo response was very high, but this study was unblinded.[25] These data suggest that as yet no comparably effective aid to smoking cessation other than bupropion SR has been tested in comparison with NRT.

Overall summary of findings for the clinical effectiveness of NRT

The effectiveness of NRT as an aid to smoking cessation has been thoroughly investigated in 113 RCTs with over 28000 participants (this figure estimated from main comparisons included in Cochrane review.[24]) The evidence indicates unequivocally that NRT as an aid to smoking cessation is more effective than placebo. The majority of the data comes from studies with NRT gum and NRT patch. However there are no data to indicate that other forms of NRT are less efficacious.

The data are much weaker for the comparison of 16hr and 24hr patches with higher doses of NRT in high-dependency smokers. The data suggest there is no real evidence to differentiate between the 24-hour and 16-hour patches in terms of effectiveness. Gradual weaning of participants off NRT has not been found to be a necessary part of the treatment regimen with NRT, but again the evidence is not strong.

Effects of different levels of motivational support have been very difficult to investigate in the confines of this review. The pooled estimates of effectiveness calculated in the Cochrane Review suggest that NRT is effective with only minimal support (low-intensity support).[24] The pooled estimate of effectiveness was not greatly different with high-intensity support. The lack of a direct comparison between low and high-intensity support with NRT precludes any definite conclusions being drawn.

The evidence suggests that the setting in which NRT is used is not critical to its effectiveness as an aid to smoking cessation. Unfortunately there are no direct comparisons from which to draw firmer conclusions.

Evidence for increased effectiveness with combinations of NRT compared with monotherapy NRT is not strong. Whilst some combinations may be useful, further data are required. NRT may be less effective than bupropion SR, but again, further data are required. With the exception of bupropion SR no other active intervention has been demonstrated to be comparable in effectiveness to NRT.

4.1.2 Bupropion SR

Two systematic reviews,[23, 40] two newly identified published RCTs and four newly identified unpublished trials[31, 32, 42, 43] and three sets of additional unpublished data[41, 43, 44] for three of the published trials[45, 46, 50] were also identified. Where appropriate the results from newly identified RCTs have been combined with the studies included in the Cochrane Review.

4.1.2.1 Systematic reviews

Description of systematic reviews

One Cochrane Review[40] and one systematic review in the form of a US Public Health Service report[23] were identified. The US report included only articles published in peer review journals between 1 Jan 1975 and 1 Jan 1999 and therefore is less comprehensive and less up to date than the Cochrane Review. Thus, only the Cochrane Review[40] has been used as a source of effectiveness data for bupropion SR in this report

The Cochrane Review assesses the effectiveness of antidepressant medications in aiding long term smoking cessation.[40] It includes five trials with bupropion SR as the main intervention. These are listed in Appendix 9.12. The RCTs have a primary outcome measure of smoking abstinence, which was assessed at a minimum of 6-months follow-up. One study

explored bupropion SR for relapse prevention compared to placebo.[46] In addition only one study compared bupropion SR directly with NRT. [39]

Two studies included in the Cochrane Review evaluated bupropion SR 300 mg/day compared with placebo,[47] [48] All participants also attended smoking cessation and relapse prevention meetings. A multicentre study evaluated sustained release (SR) bupropion in doses of 100 mg/day, 150 mg/day or 300 mg/day against placebo for seven weeks.[49] The main publication for this study reported point prevalence abstinence rates.[49] Continuous abstinence rates at 12 months were provided by GlaxoWellcome. A second multicentre study compared a combined treatment of 300 mg bupropion SR plus the nicotine transdermal patch to bupropion SR alone and patch alone and placebo in a factorial design.[49] One study has evaluated bupropion SR for relapse prevention in people who had quit during seven weeks of open label bupropion SR therapy.[46] In the treatment group bupropion SR was provided for a further 45 weeks. In all of the trials, included in the Cochrane Review, participants were not depressed at study entry, but may have had a past history of depression.[40]

In the majority of cases it was not clear what level of motivational support participants received in addition to their bupropion SR. therapy i.e. how much counselling and advice and support smokers received to assist them in their attempt to give up smoking.[40] For one study the method of allocation was considered adequate to ensure against selection bias, whereas for the other four, insufficient details were provided to make a judgement. All five studies used continuous abstinence as their definition of smoking cessation.

Quality of systematic reviews

The Cochrane Review appeared to be a good quality systematic review.[40] The searches conducted for the review were comprehensive for both published and unpublished literature. The inclusion criteria for study design, participants, intervention and outcomes all related to the purpose of the review and they were applied independently by two authors. The validity of the studies were checked formally according to specified criteria and applied independently by two authors, however, validity was not really taken into account in the review. Data extraction was performed independently by more than one author and individual study details are presented in the review. Appropriate meta-analyses with test for heterogeneity have been performed and the results presented in full.

4.1.2.2 Newly identified RCTs

Description of newly identified RCTs

Three newly identified published RCTs were identified.[45, 50, 51] In addition four newly identified unpublished trials[31, 32, 42, 43] and three sets of additional unpublished data[41, 43, 44] for three of the published trials[45, 46, 50] were also identified. These all included comparisons with placebo, except for one study that compared bupropion SR with NRT gum (4 mg).[31] The setting for most studies was unclear. The newly identified studies included some degree of motivational support, usually brief counselling at each study visit.

Quality of newly identified RCTs

Full details are presented in Appendix 9.8. One of the newly identified published studies randomised participants via a randomisation code (block randomisation) provided by the sponsoring company, though it was unclear whether intervention assignment was adequately concealed.[45] A second study randomised participants using a 1:1 ratio via a central code kept by the company and concealment of allocation appeared adequate.[50] The other study did not report any details of the randomisation procedure.[51] All three studies stated the number of participants randomised, outlined eligibility criteria, and reported comparable groups at baseline. One study was underpowered[51] and no sample size calculations were reported in one other study.[45] The sample size of the third study[50] was adequate to detect a difference between a 20% abstinence rate in the placebo group and a 35% rate in the bupropion SR group at the 5% level with 80% power.[50] All three studies are reported as 'double-blind', although success of blinding was not checked. Blinding may have been compromised in one study[50] because participants had received bupropion SR previously and therefore, may have been able to detect whether they were receiving active or placebo. All studies clearly reported withdrawals. It was clear in two of the studies that an ITT analysis had been undertaken.[45, 50] Continuous abstinence was defined as a self-report of no smoking and a CO level less than 10ppm in all three studies. In two studies[45, 50] participants received personalised counselling at the start of the study and at each clinic visit during the treatment phase. Participants in the other study also received personalised counselling sessions, but in addition were paid $100 for participating in the study.[51]

Details of the four newly identified, unpublished trials,[31, 32, 42, 43] cannot be discussed for reasons of commercial confidentiality.

4.1.2.3 Clinical effectiveness results from systematic reviews and newly identified RCTs of bupropion SR

All the results presented in this section are those derived from systematic reviews which have been updated with newly identified RCTs where available.

The effectiveness of bupropion SR versus placebo to aid smoking cessation

Details of the three newly identified published RCTs of bupropion SR versus placebo to aid smoking cessation[45, 50, 51] are summarised below and presented in Appendix 9.6.2.

RCT by Tashkin and colleagues[45]

This double-blind trial included 404 participants, aged 35 years or older with mild to moderate chronic obstructive pulmonary disease (COPD). Three months abstinence rates were as follows: bupropion SR, 18% (36/204) and; placebo, 10% (20/200). At the 6 month follow-up, abstinence rates for bupropion SR were 16% (32/204) and 9% (18/200), respectively, giving an OR 1.88 (95% CI: 1.02, 3.48).

RCT by Gonzales and colleagues[50]

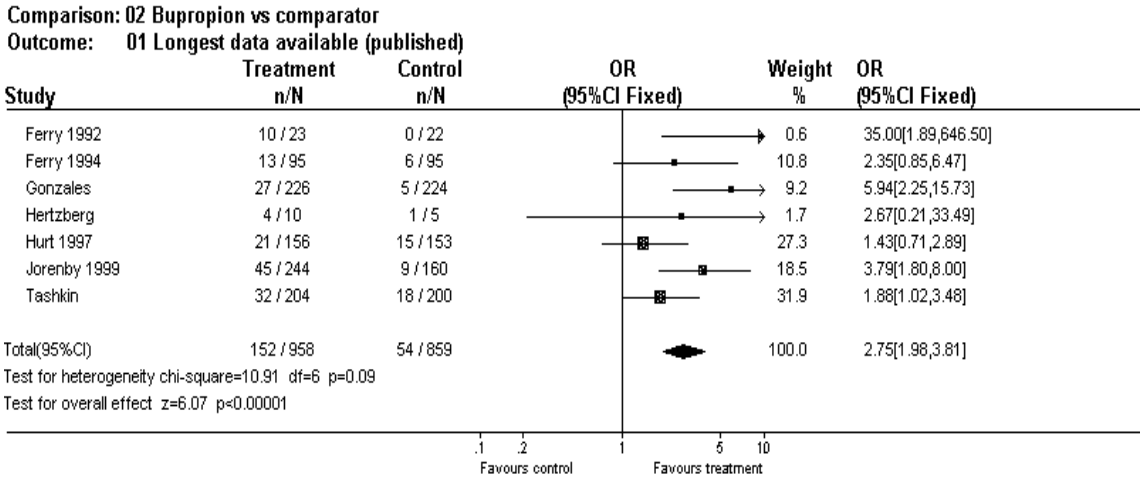
This was a multicentre, randomised, parallel-group, double-blind, placebo-controlled one year study of participants who had previously failed to abstain from smoking whilst taking bupropion SR. At 6 months, abstinence rates in the bupropion SR and placebo groups were 12% (27/226) and 2% (5/224) resepctively. In this study the response in the placebo group was particularly low, resulting in a large statistical difference between active and placebo in favour of bupropion SR. As all the participants had taken bupropion SR in the past, it seems probable that a high proportion of them would have been able to recognise that they had been given placebo and hence failed to gain any placebo effect. An alternative reason for the findings of this study is that the overall success rate may be low in those who have tried to stop smoking many times.

RCT by Hertzberg and colleagues[51]

This trial included 15 participants with a primary diagnosis (DSM-IV criteria) of post-traumatic stress disorder.[51] At 3 months (12 weeks), 60% (n = 6) of the bupropion SR group had sustained abstinence compared to 20% (n = 1) in the placebo group. At the 6 month assessment abstinence rates for bupropion SR were 40% (n = 4) and 20% (1/5) in the placebo group.

The studies already included in the Cochrane Review have been pooled with the newly identified published RCTs. Comparisons were made pooling all results obtained at the longest follow-up (minimum 6 months) and separately for those obtained at 12-months follow-up. The results of these meta-analyses are given in Figures 1 and 2.

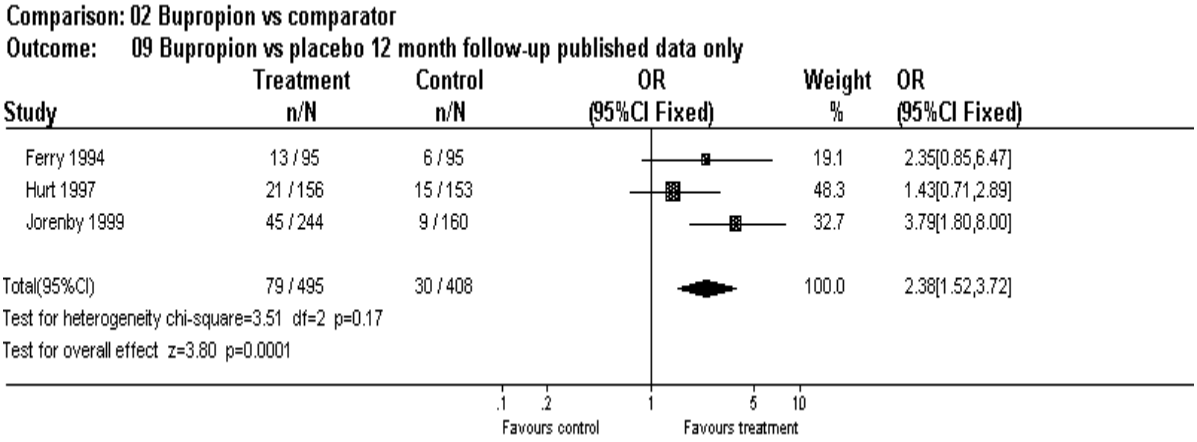
Figure 1. Abstinence from smoking for bupropion SR versus placebo for 6mth and 12mths (combined) smoking cessation: Forest plot with abstinence rates and pooled odds ratios (published data only)



If the results are pooled using a random effects model the odds ratio for bupropion SR versus placebo is 2.76 (95% CI: 1.67, 4.56).

Although the specific details of the unpublished trials cannot be presented in this report for reasons of commercial confidentiality, this restriction does not apply to an overall summary of the data. If the unpublished studies are included the result is OR 2.52 (95% CI: 1.99, 3.19) or using a random effects model, OR 2.45 (95% CI: 1.72, 3.49).

Figure 2. Abstinence from smoking for bupropion SR versus placebo 12months smoking cessation: Forest plot with abstinence rates and pooled odds ratios (published data only)



If the results are pooled using a random effects model the odds ratio for bupropion SR versus placebo is 2.31 (95% CI: 1.25, 4.28).

Although the specific details of the unpublished trials cannot be presented in this report for reasons of commercial confidentiality, this restriction does not apply to an overall summary of the data. If the unpublished studies are included the result is OR 2.21 (95% CI: 1.66, 2.94) or using a random effects model, OR 2.20 (95% CI: 1.46, 3.30).

The effectiveness of bupropion SR versus placebo in subgroup populations

a) Smokers with COPD

The effectiveness of bupropion SR versus placebo in smoking cessation was studied in a single RCT.[45] This study has been described above (RCT by Tashkin and colleagues). The effectiveness of bupropion SR in this population was generally comparable to that in the general smoking population.

b) Smokers with cardiovascular disease

The effectiveness of bupropion SR in smokers with established stable cardiovascular disease has been investigated in one study, as yet unpublished.[32]

c) Smokers who had failed to achieve abstinence with a previous course of bupropion SR

The effectiveness of bupropion SR in smokers who had previously failed to achieve abstinence from smoking despite treatment with bupropion SR has been investigated in one study.[50] This study has been described previously. The abstinence rate at 6 months was statistically significantly better in the bupropion SR group than in the placebo group (12% (27/226) and 2% (5/224) respectively), although the response in the placebo group was particularly low.

Summary of findings of bupropion SR versus placebo

The pooled estimates of effectiveness for bupropion SR versus placebo indicate clearly the effectiveness of bupropion SR. There is no real difference in the results whether all durations of follow-up are considered or just those for 12 months.

The evidence from a single study indicates that the effectiveness of bupropion SR in smokers with chronic obstructive pulmonary disease (COPD) appears to be comparable with

that in the general population of smokers at 6-month follow-up. In smokers who had previously failed to achieve abstinence from smoking despite treatment with bupropion SR, the treatment difference between bupropion SR and placebo is comparable with that seen in other studies, although the actual abstinence arates achieved were lower.

Effect of clinical setting on effectiveness of bupropion SR

There are not a sufficient number of studies to warrant an investigation of the effect of clinical setting on the effectiveness of bupropion SR. Most studies appear to be conducted in clinics with smokers recruited by advertisement.

Bupropion SR versus other active treatments

In clinical trials bupropion SR has been compared with NRT,[31, 39] but not with any other active intervention for smoking cessation. One of the comparisons of bupropion SR with NRT has been published[39] and was included in the Cochrane review.[40] This study was a randomised, placebo-controlled, double-blind, double-dummy parallel group comparison. A second unpublished study compared NRT gum (4 mg) with bupropion SR.[31] It should be noted that these two studies are also discussed in the section on effectiveness of NRT.

Table 5 presents the analysis from the Cochrane Review, which is based on a single study[39]

Table 5. Comparison between NRT patch and bupropion SR

Comparison	Proportion of abstainers in first group	Proportion of abstainers in second group	Odds ratio (95% CI fixed effect model)
Bupropion SR versus NRT patch	45/244	24/244	2.07 (1.22, 3.53)
Bupropion SR plus patch versus NRT patch	55/245	24/244	2.65 (1.58, 4.45)
Bupropion SR plus patch versus bupropion alone	55/245	45/244	1.28 (0.82, 1.99)

The ORs favour bupropion SR, suggesting that bupropion SR is more effective than NRT. There is a tendency for the combination of bupropion SR and NRT to produce higher absolute abstinence rates, but these findings were not statistically significant. These findings should be treated with some degree of caution as they are only based on a single RCT.

Summary of findings of bupropion SR versus other active treatments

The available data from a single published study suggest that bupropion SR may be more effective than NRT patch. Given the limited data available, no firm conclusions can be drawn regarding the relative efficacy of bupropion SR and NRT in smoking cessation.

Bupropion SR used to prevent relapse

In a trial of bupropion SR therapy for relapse prevention (included in the Cochrane Review) an initial benefit from continued therapy was no longer significant one-year after the end of therapy. [46]

Overall summary of findings for the clinical effectiveness of bupropion SR

There is clear evidence that bupropion SR is more effective than placebo in the general smoking poulation. There is evidence from a single study that bupropion SR is as effective in smokers with chronic obstructive pulmonary disease (COPD) as in the general smoking population. Evidence to support the superiority of bupropion SR over NRT for smoking cessation is weak and further double-blind RCTs are required. Evidence from a single trial does not support the use of bupropion SR in the prevention of relapse in people who have stopped smoking.

4.2 ADVERSE EVENTS AND SAFETY

In this section of the review there is some overlap between the adverse effects data reported in systematic reviews and in individual studies. Consequently, the information from systematic reviews will be discussed first, followed by that from individual studies.

4.2.1 Adverse events and safety of NRT

Two systematic reviews,[24, 52] plus a total of 63 individual studies (see Table 6 for breakdown of references by study design) were identified for inclusion in the review. The individual studies consisted of 18 RCTs, three non-RCTs, one case-control study, 19 uncontrolled studies, five surveillance studies (three published, two unpublished) and 17 case reports or case series. Within the individual studies identified (irrespective of design), there were a total of nine studies whose primary objective was to assess the incidence of adverse events with NRT, 28 that described investigations related to some specific aspect of the safety profile of NRT (e.g its effect on cardiovascular function) and four related to the safety of NRT in pregnancy.

Table 6. Summary of references included for adverse events and safety of NRT

	Objective of or Type of Study					
Design	**Incidence of AEs**	**Investigating specific aspects of the safety profile**	**Pregnancy**	**Surveillance**	**Individual Cases of AEs**	**TOTAL**
RCT	**n=1** 53	**n=15** 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68	**n=2** 69 29			**N=18** 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 29
Non-RCT		**n=3** 70 71 72				**n=3** 70 71 72
Uncontrolled	**n=7** 73 74 75 76 77 78 79	**n=10** 80 81 82 83 84 85 86 87 88 89	**n=2** 90 91			**n=19** 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91
Case-control	**n=1** 92					**n=1** 92
Surveillance				**n=5** 93 94 95 96 97		**n=5** 93 94 95 96 97
Case reports or series					**n=17** 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114	**n=17** 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114
TOTAL	**n=9** 53 73 74 75 76 77 78 79 92	**n=28** 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 70 71 72 80 81 82 83 84 85 86 87 88 89	**n=4** 69 29 90 91	**n=5** 93 94 95 96 97	**n=17** 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114	**n=63** 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 29 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114
Note: some studies published in additional references: [64] published as [115], [81] as [116], [93] as [117] and [69] as [118]						

4.2.1.1 Systematic reviews of NRT

Description of systematic reviews of NRT

Two systematic reviews that included data on the adverse events and safety of NRT were identified.[24, 52] One was a Cochrane Review (most recently updated July 2001)[24] and the other a meta-analysis of adverse events associated with NRT.[52] Details are given in Appendix 9.7.1.6.

Quality of systematic reviews of NRT

The quality of the Cochrane Review has previously been discussed in section 4.1.1.1. In terms of adverse event and safety data it summarised very briefly only those adverse events reported in RCTs in which NRT was used for smoking cessation. No attempt was made to synthesise quantitatively the incidence of the various side effects reported with the different NRT preparations.

The other review[52] was not carried out in a truly systematic manner as studies were identified through limited searching (the Medline database and information supplied by only one manufacturer (Ciba Geigy)). By including both published and unpublished data from the manufacturer, the review did reduce the risk of publication bias. Papers were only considered if they were published prior to 1 Dec 1996. The validity of studies was not formally assessed, however, only RCTs with a minimum of 20 participants per treatment arm were included, so the data should be of reasonable quality. To eliminate the possibility of bias when measuring subjective outcomes only placebo-controlled trials were considered. Details of the individual studies were not presented. The study data were pooled using a meta-analysis with tests for heterogeneity. No specific criteria for participants were specified and not all were smokers or using the nicotine patch for smoking cessation (e.g. some participants were in studies of nicotine effectiveness in ulcerative colitis).

Adverse events data from systematic reviews of NRT

The Cochrane Review reported that the major side effects associated with nicotine gum were hiccups, gastrointestinal disturbances, jaw pain, and orodental problems.[24] The only side effect that appears to interfere with use of the patch is skin sensitivity and irritation; this may affect up to 54% of patch users, but it is usually mild and rarely leads to withdrawal of patch use. The major side effects reported with the nicotine inhaler and nasal spray are related to local irritation at the site of administration; e.g. throat irritation, coughing, and oral burning with the nicotine inhaler and nasal irritation and runny nose with the nasal spray. Nicotine sublingual tablets have been reported to cause hiccups, burning and smarting sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers. The review found no evidence that serious adverse events were more common in smokers in the NRT treatment group. In addition, the incidence of events related to cardiovascular disease such as an increase in angina severity did not differ according to whether or not patients received NRT.

The overview included a meta-analysis that estimated the frequency of adverse effects associated with the NRT patch.[52] A total of 34 RCTs plus one study on contact sensitisation were included in this meta-analysis. These studies are listed in Appendix 9.12.

The meta-analysis included a total of 3216 participants treated with NRT patch and of these, 127 (approximately 4%) withdrew due to adverse events. This compared with 55/2164 (2.5%) of those on placebo experiencing adverse events that resulted in withdrawal. It should be noted that the proportion of patients with adverse events or who withdrew due to adverse events will be an inflated estimate due to the fact that this review excluded studies that did not report adverse event.

The adverse events reported in the studies included in the meta-analysis were (by classification): cardiovascular (myocardial infarction, stroke, tachycardia, palpitations, angina, arrythmia, hypertension); gastrointestinal (nausea, vomiting, constipation, diarrhoea, dyspepsia, unimproved ulcerative colitis, musculoskelatal symptoms); respiratory (asthma, bronchitis, other respiratory symptoms); urogenital symptoms. Details of their incidences are presented in Table 7.

Table 7. Adverse events associated with the use of the NRT patch[52]

Adverse event	Proportion of participants reporting an adverse event		Relative risk versus placebo, CI, homogeneity
	NRT patch	Placebo	
Myocardial infarction	3/36 (1%)	3/362 (1%)	Incidence of MI low possibly because people at risk would not be treated with NRT.
Stroke	1/354 (0.3%)	2/357 (1%)	RR versus placebo 0.54 (95% CI: 0.02, 6.73) homogeneity p=0.38).
Tachycardia	2/239 (1%)	none reported.	
Palpitations	2/446 (0.4%)	8/451 (2%).	RR versus placebo 0.26 (95% CI: 0.04, 1.10) Homogenety p= 0.54)
Angina	1/239 (0.4%)	1/238 (0.4%)	RR versus placebo1.00 (95% CI: 0.025, 39.0)
Arrhythmia	11/406 (3%)	9/411 (2%)	RR versus placebo 1.26 (95% CI: 0.56, 2.87) RR per 21 mg nicotine 1.43 (95% CI: 0.48, 4.24) Homogeneity p= 0.24
Hypertension	8/354 (2%)	5/357 (1%)	RR versus placebo 1.60 (95% CI: 0.52, 5.48) RR per 21 mg nicotine 1.79 (95% CI: 0.50, 6.45) Homogeneity p=0.20 Reported in2 trials only
Nausea and vomiting	141/2670 (5%) Reported in 11 studies	99/2238 (4%)	Range of RR 0.38 to 7.00 Homogeneity p=0.0012
Constipation, diarrhoea, dyspepsia	60/1336 (4%)	54/1282 (4%)	RR versus placebo 1.08 (95% CI: 0.75, 1.55) RR per 21 mg nicotine 1.18 (95% CI: 0.87, 1.59) Homogeneity p=0.25
Unimproved ulcerative colitis	32/75 (43%)	treatment 45/77 (58%)	RR versus placebo 0.73 (95% CI: 0.54, 1.01) Homogeneity p=0.68 Reported in 2 trials. Not really an adverse event: indicates lack of efficacy of nicotine in treating ulcerative colitis
Musculoskeletal symptoms	21/513 (4%)	11/421 (3%)	RR versus placebo 1.48 (95% CI: 0.71, 3.07) RR per 21 mg nicotine 1.27 (95% CI: 0.91, 1.77) Homogeneity p=0.55
Asthma	0/115 (0%)	2/119 (2%) reported in one study only	
Bronchitis	9/115 (8%)	5/119 (4%)	RR versus placebo 1.91 (95% CI 0.63, 6.54) RR per 21 mg nicotine 2.12 (95% CI: 0.62, 7.27) reported in one trial
Respiratory symptoms other than asthma or bronchitis	23/892 (3%)	2/497 (0.4%)	RR versus placebo 5.68 (95% CI: 1.64, 38.7) RR per 21 mg nicotine 5.96 (95% CI: 1.79, 19.9) Homogeneity p=0.55
Urogenital symptoms	0/115 (0%)	1/199 (1%)	
Neurological symptoms	4/115 (3%)	1/159 (1%)	RR versus placebo 3.80 (95% CI: 0.51, 10.6) Homogeneity p=0.57 Reported in 2 trials
Localised skin irritation	884/3584 (25%)	410/3102 (13%)	Range of RR 1.10 tp 5.57 Homogeneity p=0.011 Reported in 23 trials
Chest pain	11/1228 (1%)	7/1200 (1%)	RR versus placebo 1.52 (95% CI: 0.60, 3.85) RR per 21 mg nicotine 2.02 (95% CI 0.69, 5.94) Homogeneity p=0.50.
Headache	264/2624 (10%)	206/2133 (10%)	RR versus placebo 1.06 (95% CI 0.89, 1.25) RR per 21 mg nicotine 1.02 (95% CI: 0.87, 1.19)

	Proportion of participants reporting an adverse event		
			Homogeneity p=0.46
Fatigue, malaise	8/414 (2%)	9/358 (3%)	RR versus placebo 0.63 (95% CI: 0.25, 1.61) RR per 21 mg nicotine 0.93 (95% CI: 0.26, 3.33) Homogeneity p=0.16
Sweating	51/164 (31%)	46/164 (28%)	RR versus placebo 1.11 (95% CI: 0.81, 1.52) RR per 21 mg nicotine 1.23 (95% CI: 0.80, 1.90) Homogeneity p=0.095
Dizziness	117/1599 (7%)	87/1104 (8%)	RR versus placebo 1.00 (95% CI: 0.78, 1.28) RR per 21 mg nicotine 1.04 (95% CI 0.72, 1.48) Homogeneity p=0.38
Sleep disturbance	280/1490 (19%)	117/1451 (8%)	RR versus placebo 2.31 (95% CI 1.89, 2.83) RR per 100 mg nicotine 2.03 (95% CI: 1.71, 2.41) Homogeneity p=0.22
Alteration in taste	27/1101 (2%)	16/1043 (2%)	RR versus placebo 1.55 (95% CI: 0.82, 2.93) RR per 21 mg nicotine 1.24 (95% CI: 0.65, 2.37) Homogeneity p=0.15
Alteration in mood mental status	85/382 (22%)	61/380 (16%)	RR versus placebo 1.39 (95% CI: 1.08, 1.78) RR per 21 mg nicotine 1.55 (95% CI: 1.10, 2.19) Homogeneity p=0.081
Urticarial reaction	0/115 (0%)	1/119 (1%)	
Unspecified adverse effects	106/822 (13%)	64/598 (11%)	RR versus placebo 1.24 (95% CI: 0.95, 1.63) RR per 21 mg nicotine 1.29 (95% CI: 0.92, 1.79) Homogeneity p=0.63

Compared with placebo the adverse events that have an increased relative risk with NRT are respiratory symptoms other than asthma or bronchitis, localised skin irritation, sleep disturbances, and alteration of mood.

Summary of findings from systematic reviews of NRT

Localised skin reactions are to be expected with the NRT patch. Sleep disturbances and alteration of mood could be symptoms of nicotine withdrawal rather than a true adverse effect of therapy. Overall, evidence from both systematic reviews suggests that the adverse effects of NRT are specific to the type of NRT used, with little overlap between the different types of NRT therapy.

4.2.1.2 Studies whose primary objective was to investigate the incidence of adverse events with NRT

Description of studies whose primary objective was to investigate the incidence of adverse events with NRT

A total of nine published studies whose primary objective was to investigate the incidence of adverse events with NRT were identified. [53, 73-79, 92] Of these, one was an RCT,[53] one was a case control study,[92] and seven were uncontrolled studies,[73-79] one of which reported the adverse event data for a subset of what was originally a RCT.[77]

Quality of studies whose primary objective was to investigate the incidence of adverse events with NRT

The quality assessment data are presented in full in Appendix 9.8. The one RCT study[53] was of good quality except for some lack of clarity in reporting withdrawals. Of the uncontrolled studies, it was unclear in four studies[73, 75, 76, 78] if the sample size was appropriate; participant accountability was unclear in two studies;[74, 75] statistical methods not described or unclear in four studies;[74, 76-78] in one study the design was not appropriate[73] and in another it was unclear if the measurements were appropriate.[78] One study consisted of data collected from a group of participants who had been one arm of an RCT, who responded to NRT and who were still using NRT after a period of one year.[77]

Adverse events data from studies whose primary objective was to investigate the incidence of adverse events with NRT

Details of individual studies are presented in Appendix 9.7

a) NRT patch

There was one randomised, placebo-controlled, double-blind study.[53] Participants were smokers with known coronary artery disease. Of the 294 participants randomised to NRT, 48 (16.3%) reported at least one serious adverse event. These are summarised in Table 8.

Table 8. Number of patients experiencing at least one serious adverse event

Adverse event	NRT patch group		Placebo group	
	All patients (n=294)	Smoking	All patients (n=290)	Smoking
Death,	1	1	6	3
Myocardial infarction	0	0	1	1
Cardiac arrest	1	0	1	0
Admission for increased severity of angina	7	4	10	5
Admission for arrhythmia,	5	4	3	3
Admission for congestive heart failure	2	0	2	1
Admission for peripheral vascular disease	3	1	5	3
Admission for cerebrovascular disease,	4	3	3	2
Admission for other reasons	16	6	13	9
Outpatient visit for increased severity of atherosclerotic cardiovascular disease	12	7	7	5
Sleep disturbance	10		6	
Skin reaction	6		3	
Gastrointestinal distress	5		6	
Other	15		12	

The one case-control study to investigate a possible link between NRT patch use and occurrence of myocardial infarction.[92] found that 3/653 cases had used NRT patch within the seven days prior to their hospital admission for MI (0.46% this was compared to the patch use in the controls (30/2990, 1%) (OR=0.46 (95% CI: 0.09, 1.47)). These findings are consistent with the physiological and pharmacodynamic properties of nicotine patches and with other studies that suggest no serious adverse cardiovascular effects among patch

users. Risk factors for MI were statistically significantly more common in the cases than the controls. The analysis incorporated adjustment of confounders. The findings of this study suggest that use of the NRT does not precipitate MI in these high-risk individuals.

A large uncontrolled follow-up study of 1481 adult investigated the adverse events associated with the 21 mg/24 hour patch.[74] The participants were adult smokers, mean age 41 years (SD 11) and 56% of them were female. Of the 1392 participants for whom follow-up data were available 478 experienced a cutaneous application site reaction; 36 a serious one (2.6%). There was no association between pre-existing skin disorders and moderate-severe application site reactions (Hazard ratios <1.3, p>0.3). Other adverse events reported in the study were: any sleep problem 669/1393 (48.1%); dreaming 414/1392 (29.7%); other sleep disturbance 447/1392 (32.1%). Overall, 61/1392 (4.3%) participants reported serious sleep problems.

One small study of only 40 participants recruited heavy smokers (mean Fagerstrom score 7.3) who were then treated with NRT patch (44 mg) for four weeks followed by NRT patch (22 mg) for a further four weeks.[73] The adverse events reported with this high-dose regimen were erythema 52.5%; erythema with oedema 15.0%; erythema with vesicles 5.0%; bullae/erosions 2.5%; itching only 7.5%. Difficulty in sleeping was reported by 13 participants (32.5%) in total. Nine participants (25%) reported experiencing vivid/unusual dreams during the 44 mg dose period, and one participant (2.5%) reported similar effects during the 22 mg dose period. Papillary carcinoma and myocardial infarction were each reported by a single participant in each case. Other minor adverse events included mild, self-limiting cardiovascular symptoms (tight chest, racing heart, light-headedness, nausea, vomiting, headache).

Another small (22 participants) uncontrolled study investigated the safety of the NRT patch (22 mg tapering to 11 mg over eight weeks) as an aid to smoking cessation in adolescent smokers (mean age 15.9yrs; SD 1.3; range 13 to 17) who had been smoking for a mean of 2.6yrs (SD 1.6).[78] In this study 59% of participants reported a skin reaction. Other adverse events were headaches (41%), nausea/vomiting (41%), dizziness (27%), tiredness (27%) and arm pain (22%). None of these were considered serious or life threatening, nor led to the discontinuation of patch therapy.

Confidential information regarding NRT patch (Niquitin CQ®) therapy was also available in the GlaxoSmithKine submission to NICE.[97] This cannot be include in this review for reasons of commercial confidentiality.

Summary of adverse events findings for NRT patch

These studies suggest that cardiovascular function is not compromised by the use of the NRT patch. As indicted in other studies skin reactions are the most common adverse events associated with NRT patch use.

b) NRT nasal spray

Two small prospective uncontrolled studies of the NRT nasal spray were identified.[75, 76] One study included 50 adult smokers, who were treated with nicotine nasal spray, 1 to 2 mg/hour for only seven days.[75] Of the 50 participants, 47 (94%) reported at least one adverse event. Symptoms reported by 10% or more of participants were headache (n=17), burning sensation on nose, throat or unspecified areas (n=14), watering eyes (n=13), nasal irritation (n=12), throat irritation (n=12), sneezing (n=9), runny nose (n=9), cough (n=7), and awakening during the night or early awakening (n=5). One patient suffered a stroke (72 year old female). One patient experienced exacerbation of old emotional problems and one participant experienced abdominal pain and subsequently underwent cholecystectomy. The latter two events were not considered related to use of the spray.

The other study of nasal spray included only 40 adult smokers with a well documented history of chronic rhinitis and/or chronic sinusitis.[76] Seventy-nine percent of the participants were still using the spray at the 20-week visit. Withdrawals due to adverse events were not reported. The results are presented in Table 9. Further details are given in Appendix 9.7.

Table 9. Incidences % of adverse events reported during the study.

Adverse event	% of adverse events		
	week 1	week 6	Week20
Nasal irritation	78	51	51
Bleeding in the nose	22	21	20
Irritation in the throat	62	30	10
Sneezing	78	51	65
Irritation in the eyes	58	18	28
Cough	54	27	17
Nausea	25	6	10
Sweating	47	28	17
Headache	47	24	17

Summary of adverse events findings for NRT nasal spray

The adverse effects associated with the use of the nasal spray are primarily local irritation. Unsurprisingly participants with a pre-existing chronic rhinitis or sinusitis reported a high incidence of nasal irritation and other nasal symptoms. For the majority of participants these effects did not necessitate their stopping the use of the nasal spray.

c) NRT gum

Two studies that investigated the safety of the NRT gum were identified.[77, 79] One study reported mainly the effects of chewing NRT gum on nicotine levels.[79] The other study reported adverse event data for 925 participants who had entered the Lung Health Study (LHS), had been randomised to special intervention (which included NRT gum use), rather than usual care and who had achieved abstinence.[77] Neither of the studies relating to gum use is of good quality or particularly informative regarding the adverse events' profile. Further details are given in Appendix 9.7.

Summary of adverse events findings for NRT gum

Neither of the studies relating to gum use is of good quality or particularly informative regarding the adverse events' profile.

Summary of findings from studies whose primary objective was to investigate the incidence of adverse events with NRT

Overall, data from these studies indicate that, as expected, skin irritation is the most common adverse effect associated with the NRT patch and nasal irritation with the NRT nasal spray. No useful data were available from these studies regarding NRT gum or lozenge/sublingual tablet or NRT inhaler.

4.2.1.3 Studies investigating specific aspects of the safety profile of NRT

Description of studies investigating specific aspects of the safety profile of NRT

Twenty-eight studies were identified that described specific investigations related to some aspect of the safety profile of NRT, addressed the effects of NRT on cardiovascular function, blood lipid profile, endocrine system, cutaneous inflammatory response, endothelial dysfunction, platelet activation, glucose tolerance, body weight change, and the oral mucosa.[54-68, 70-72, 80-89]

Quality of studies investigating specific aspects of the safety profile of NRT

Given the broad range of questions addressed by these studies it is not surprising that they vary greatly. Most of the RCTs in this section were double-blind, but one was single-blind,[56] one was unblinded[68] and for four studies the level of blinding was unclear.[60, 61, 65, 119] Overall, the quality of the RCTs was limited: mainly in terms of accountability and analysis. Participant accountability was poor in seven studies[56, 59, 61, 64, 66-68] and only two were clearly analysed using an ITT analysis.[54, 65] Generally the quality of the uncontrolled studies

appeared adequate, the main problem for many being an uncertainty regarding the sufficiency of the sample size. [81-83, 87-89] The inherent weaknesses of this type of study must be borne in mind.

Adverse events data from studies investigating specific aspects of the safety profile of NRT

a) Effects of NRT on cardiovascular function

A total of 16 studies that investigated the effect of NRT on cardiovascular function were identified.[54, 55, 57-60, 62-64, 70-72, 84-87, 115] (It should be noted that references [64] and [115] refer to the same study) These included nine RCTs,[54, 55, 57-60, 62-64, 115] three non-randomised controlled trials[70-72] and six uncontrolled studies.[84-87]

Six of the RCTs included healthy individuals.[54, 55, 58, 59, 62, 63] All were placebo-controlled and double-blind except one[63] and investigated the effect of NRT on blood pressure. The number of participants in these studies ranged from 10 to 50. Three studies used the NRT patch,[55, 59, 62] one a nasal spray[54] and two NRT gum.[58, 63] Three of the studies were performed in smokers,[55, 62, 63] one in non-smokers,[54] one in a combination of smokers and non-smokers,[59] and one in users of smokeless tobacco.[58] In non-smokers NRT was shown to acutely increase systolic blood pressure (SBP) and mean arterial blood pressure (MABP), but not diastolic blood pressure (DBP) or heart rate (HR). [54] In smokers application of the NRT patch produced a moderate acute increase in MABP, but over a period of 14 days had no effect on SBP and may very slightly reduce DBP.[55, 62, 63] In smokeless tobacco users use of nicotine gum had no effect on BP or heart rate.[58] The one comparison with smoking cigarettes found that no acute cardiovascular effects were associated with the use of NRT gum, whereas cigarette smoking induced increases in CO levels, HR, SBP, and DBP.

Two of these RCTs also examined the effect of NRT on cardiac conduction.[55, 62] The largest (50 participants) and longest study (two weeks treatment with 14 mg and 21 mg patches) reported no significant differences in ECG parameters, heart rate or BP between treatment and placebo groups.[62] The other study, a crossover design with 27 participants reported that the RR interval appeared significantly reduced.[55] In both studies the smoking and nicotine patch groups were compared to placebo. The RR variability appeared to be reduced by smoking and to a lesser extent by use of nicotine patches. This suggests that nicotine-patch treatment leads to an autonomic state intermediate between that observed during smoking or placebo patch administration, reflective of only minor disturbances of autonomic cardiac control.

There were three RCTs in patients with cardiovascular disease.[57, 60, 64, 115] Two were double-blind, placebo-controlled studies conducted in patients with coronary artery disease (CAD) including 77 to 106 participants.[57, 64, 115] The other RCT was a small, unblinded study in participants with suspected CAD.[60] No details of the method of allocation were given so it is not possible to determine if there might have been selection bias.

The first two RCTs,[57, 64, 115] found no effect of NRT patch on resting heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), signs of ischaemia on ambulatory ECG monitoring or nocturnal arrhythmia. One study reported fewer angina attacks.[57]

The third RCT[60] found that smoking a cigarette after 12 hours abstinence decreased coronary artery luminal diameter, but that further smoking or use of NRT nasal spray did not reduce the luminal diameter further. Due to the design of this study the effect of NRT on coronary artery diameter was not assessed

Details of the non-randomised controlled trials[70-72] and the uncontrolled studies that investigated the cardiovascular effects of NRT are given in Appendix 9.7[63, 70, 84-87] Their findings generally support those of the RCTs, however, as they are small studies and the reliability of their findings is limited, they have not been discussed in further detail.

Summary of effects of NRT on cardiovascular function

Overall, the RCTs do not suggest any significant adverse cardiovascular effects of NRT in healthy adults, either in terms of the effect on blood pressure or conduction. There is also no evidence to suggest any short-term adverse effects of NRT in patients with CAD. The cardiovascular effects of NRT have to be considered in the context of smokers self-administering nicotine and exposing themselves to the other harmful constituents of tobacco smoke.

b) Effects of NRT on blood lipid profile

The effects of NRT on the blood lipid profile were investigated in two studies.[58] One was a randomised, double-blind placebo-controlled study that included 56 users of smokeless tobacco.[58] The other was an uncontrolled open label study of 27 ex-smokers[88] After five or eight weeks of treatment no changes were seen for total cholesterol, low density lipid (LDL) cholesterol, high density (HDL) cholesterol or triglycerides, in either study.

Summary of effects of NRT on blood lipid profile

The fact that no changes in blood lipids were seen after NRT treatment would suggest that the 'normalisation' of HDL cholesterol expected after quitting smoking was not seen in these studies; possibly due to NRT. Furthermore, one of these studies was conducted in participants using smokeless tobacco and it is possible that HDL cholesterol is not abnormal in users of smokeless tobacco, thereby affecting the outcome.

c) Endothelial function

A single dose crossover RCT in 21 smokers and non-smokers found that transdermal nicotine administration to non-smokers blunted the vasodilator response to bradykinin compared with that in smokers.[59] This suggests a pivotal role for nicotine in endothelial dysfunction in cigarette smokers. The small study of the acute effects of 0.5 mg nicotine spray in 14 participants undergoing cardiac catherterisation for the investigation of chest pain found that using the spray after smoking a single cigarette did not further reduce the minimal luminal diameter of non-diseased coronary artery segments.[60] Unfortunately the effects of NRT alone were not studied. In addition an RCT that compared the effects of smoking and NRT nasal spray found that flow-mediated dilation of the brachial artery was more pronounced after the cigarette than after the spray (found by ANOVA, p=0.017).[56] The authors concluded that nicotine alone causes acute endothelial dysfunction, but to a lesser extent than cigarettes.

Summary of effects of NRT on endothelial function

The effects of NRT on endothelial dysfunction appear to reflect those of nicotine acquired through smoking.

d) Effects of NRT of glucose tolerance

The effects on glucose tolerance have been investigated in a crossover-design, partially blinded, placebo-controlled RCT that included 12 participants with Type 2 diabetes mellitus.[61] Glucose tolerance was measured after smoking, after NRT patch or after placebo patch. The findings of the study indicated that overall the impairment of insulin action following cigarette smoking takes place at the level of the liver, adipose tissue, and muscle. Nicotine appears to deteriorate glycaemic control in Type 2 diabetes merely by exacerbating insulin resistance. Nicotine from a patch reduces the action of insulin but does so to a lesser extent than seen with cigarette smoking.

Summary of effects of NRT on glucose tolerance

The effects of NRT on glucose tolerance appear to reflect those of smoking, but to a lesser extent.

e) Effect of NRT in causing a cutaneous inflammatory response

Adverse cutaneous reactions are an adverse effect generally associated with the transdermal patch form of NRT (NRT patch). They have been studied in three uncontrolled studies.[66, 82, 83] One in healthy smokers,[66] one in smokers with known sensitivity,[82] and one in non-smokers.[83]

One study in 230 healthy men and women smokers, aged 18-65 years examined the effects of the NRT patch (2.5 cm^2, 12.5 mg nicotine, 3.8 mg/24 hr), when each patch was worn for 48 hours and the treatment period lasted 42 days.[66] The percentage with no reaction to the patches ranged from 8.6 to 58.1%. The percentage with faint erythema ranged from 41.9 to 90.9% and that with moderately intense erythema ranged from 0.0 to 2.7%. There were no reports of any more severe erythema. The relevance of these findings is limited to patches of the exact formulation used in the study. It is also limited by the fact that currently available patches are worn for 16 or 24 hours not 48 hours.

In a study of 14 volunteers who had all experienced cutaneous side-effects from the use of the nicotine patch (six were atopic by skin prick test)[82] a positive skin reaction to a component of the patch was seen in ten participants. Two participants had a contact urticarial reaction to 50% nicotine base, one further reacted to all three concentrations, four further had equivocal reactions. Only one equivocal reaction was seen with nicotine sulphate. Five participants had a positive allergic reaction to nicotine base. One participant only had a positive reaction to nicotine sulphate, the patch matrix and to the adhesive. These findings indicate that even in sensitive individuals not all skin reactions are allergic.

Another small uncontrolled study in ten non-smokers found that after two weeks of NRT patch wearing there was a significant reduction in cutaneous inflammatory response to sodium lauryl sulphate ($p < 0.001$), and irradiation with UV-B ($p < 0.003$).[83] In addition a reduction in reactive hyperaemia ($P<0.03$) was observed, which returned to normal after 4 weeks. There was no change in blood flow following application of topical nicotinates. These data suggest nicotine delivered by patch transiently suppresses cutaneous inflammatory response, but the clinical significance is unclear.

Summary of effects of NRT on the cutaneaous inflammatory response

The data from studies that have investigated the potential of the NRT patch to cause skin reactions is weak and provide limited information regarding the nature and preventability of these reactions. Furthermore, the generalisability of any of these data is limited, given the various formulations of patch available, and the various recommended dose regimens.

f) Effect of NRT on the oral mucosa

The effects of the sublingual nicotine tablet (2 mg nicotine) when used for up to 6 months was investigated in an uncontrolled study that included 30 healthy adult smokers, without pre-existing mouth ulcers.[81] Eight participants developed lesions on the floor of mouth. All occurred during weeks 1-6 and had healed by 6 months. Of those lesions from which a biopsy was removed (n=11), the lesions consisted of keratinised mucosa (n=1), hyperplastic mucosa (n=1), and inflammatory cells (n=4). For other sites in the mouth 15 lesions were present at baseline, falling to six at 12 months. This study was also reported in a second publication.[116]

Summary of effects of NRT on the oral mucosa

The results of this single study suggest that the incidence of mouth ulcers increases with NRT lozenges, but that they resolve with time.

g) Effect of NRT on body weight change

One study investigating the effects of NRT on weight gain in association with smoking cessation has been identified.[67] This was a RCT of participants treated with NRT gum (2 mg or 4 mg) or placebo. Only those who had achieved smoking cessation were included in the analysis: of the initial sample of 608 there were 92 (2 mg n=35; 4 mg n=40, placebo =17) eligible for this analysis at 1 year. For those participants receiving NRT gum 2 mg the mean body mass index (BMI) changed 1.2 kg/m^2 relative to a baseline of 25.3 (SD 4.3); on 4 mg gum BMI changed 1.3 kg/m^2 relative to a baseline of 28.2 kg/m^2 (SD 6.2); and on placebo the change was 1.2 kg/m^2 relative to a baseline of 26.7 kg/m^2 (SD 5.7). For those still using gum at 3 months the mean increase in BMI was 1.8 kg/m^2 in those using placebo gum compared to approximately 0.5 kg/m^2 in the two active gum groups, but by one year the difference has been eroded.

Summary of effects of NRT on body weight change

These data from a single study suggest that individuals who attempt smoking cessation with the aid of NRT may not gain as much weight in the short term but that after one year there is no effect of NRT on body weight.

h) Studies that investigated the abuse potential of NRT

A total of four studies investigated the abuse potential of NRT.[65, 68, 80, 89] Two were RCTs.[65, 68] One was unblinded and gave no details regarding the method of allocation used.[68] The other study was a partially blinded.[65] One of the RCTs studied different types of NRT.[68] The other studied different methods of NRT withdrawal.[65] The remaining two studies were uncontrolled studies,[80, 89] one being very small.[89]

The unblinded RCT included adult smokers in an investigation of the relative abuse potential of the different forms of NRT (gum, patch, spray, inhaler).[68] The results of the study are summarised in Table 10. The study found that most people manage to stop using NRT at the end of the prescribed course without discomfort.

Table 10. Measure of abuse potential with NRT[68]

Outcome measure	Number of participants			
	Gum (n=127)	Patch (n=124)	Spray (n=126)	Inhaler (n=127)
Amount of product used since last visit (week 15)	2.5(sd 2.6)	0.3 (SD 0.2)	4.8 (SD 4.0)	1.0 (SD 1.3)
Pleasantness/unpleasantness (and satisfaction) compared with cigarettes (week 4)	5 (3.2)	6.5 (3.8)	4.6 (4.0)	5.2 (4.0)
How dependent they were on their product (week 15)	22%	0%	20%	33%
Proportion of participants still using NRT (week 15)	7%	2%	10%	7%

The second RCT[65] investigated the effect of different methods of withdrawal on gum use or smoking relapse in ex-smokers who had achieved abstinence from smoking but were still using nicotine gum (2 mg) at least 6 months after starting. At the end of six weeks the proportion of participants who had not relapsed to gum or smoking was 67% (95% CI: 29.9, 92.5) for the abrupt withdrawal group, 71.4% (95% CI: 29.1, 96.3) for the taper with placebo gum group, and 60% (95% CI: 26.2, 87.8) for the taper with active gum group. The findings of this study are likely to have been influenced by the lack of blinding. Abrupt withdrawal could not be blinded compared with other interventions in this study and the placebo gum was probably not indistinguishable from active to participants who had long experience with active gum. In addition the small sample size and short follow-up were also significant limitations in this study.

Two uncontrolled studies examined the abuse potential of NRT.[80, 89] One study assessed the acute effects of NRT nasal spray or inhaler,[89] whilst the other assessed the long-term effects of NRT gum.[80] The acute study was small, including only 12 adult smokers who had been deprived of nicotine overnight prior to testing.[89] Only modest elevations on a measure of 'good' drug effects were observed with either the spray or the inhaler. These delivery

systems produced unpleasant effects of burning throat and nose, watery eyes, runny nose, coughing and sneezing. These effects might be expected to limit the abuse liability of these products, which appear to be of substantially lower abuse liability than cigarettes in experienced smokers receiving initial exposure to these products.

In the other study smokers were given Nicotine gum 2 mg for either one or three months.[80] There was evidence of withdrawal symptoms (i.e. difficulty concentrating, increased variability in reaction-time tests and decreased vigour), however, the authors conclude that the results showed minimal nicotine gum withdrawal symptoms after gum cessation, with virtually no difference in gum withdrawal between the one-month and three-month treatment groups.

Summary of effects of NRT and its abuse potential

Most individuals are able to stop using NRT at the end of treatment without discomfort, and there are no major differences between the various forms of NRT. Stopping use of NRT (gum) is not greatly eased by gradual reduction of use, rather than abrupt withdrawal. Overall, abuse potential is low.

i) Studies related to the use of NRT during pregnancy or lactation

All therapies including NRT are only prescribed for use during pregnancy if their potential benefits greatly outweigh the risk to the mother and particularly the foetus. Women who smoke are already exposing themselves and the foetus to nicotine and, therefore, there is a rationale for advocating the use of NRT if the end result can be smoking cessation. Four studies have been identified that have addressed the problem of the safety of NRT use by women attempting to stop smoking during pregnancy.[29, 69, 90, 91] One was a placebo-controlled RCT using NRT patches[29], and one was an acute, randomised, crossover comparison of NRT with smoking.[69] The other two studies were small uncontrolled studies.[90, 91] All investigated the effects of smoking compared with those of the NRT patch (21 mg). Further details are given in Appendix 9.7.

The placebo-controlled RCT[29] followed pregnant women from some point prior to the 22nd week of gestation to term. A total of 11 women did not use patches due to adverse events which included skin reaction, headache, palpitations, and nausea. Mean birth weight was 3457 g in nicotine group and 3271 g in the placebo group (mean difference 186 g (95% CI 35, 336). Among children born after 37 weeks' gestation mean birth weights were 3539 g and 3381 g respectively (mean difference 157 g 95% CI 25, 291 g). The proportion of infants with weight under 2500 g was 3% and 9% in the nicotine and placebo groups respectively (RR

0.4, CI 0.1, 1.1). Adjustment for preterm delivery, smoking habits, and other factors yielded similar results. The rate of pre-term delivery was 8% in the nicotine group and 10% in the placebo group (RR 0.8 (95% CI 0.4, 1.7)). Use of nicotine patches was low with only 17% using all the 15 mg patches and 1% using all the 10 mg patches. This data cannot reliably inform about safety or otherwise of nicotine patches in pregnancy.

The acute RCT[69] found that the plasma AUC for nicotine during patch use was 93 ng-hour/ml compared to 89 ng-hour/ml whilst smoking (p=0.77), but the measure of foetal hypoxia during patch use was not different from whilst smoking. The acute effects of nicotine on measure of foetal health are apparently similar regardless of method of administration.

The two uncontrolled studies, one with only six participants and the other 21 participants, also assessed the acute effects of the NRT patch on foetal well-being.[90, 91] The main finding in the larger of the two studies[90] was that during the four days of smoking abstinence and nicotine patch use, morning foetal heart rates were significantly reduced relative to baseline when smoking *ad libitum* was permitted. The very small, acute (8-hour) study reported no measurable differences in foetal well-being after placement of the NRT patch.

Summary of effects of NRT during pregnancy or lactation

There is only a limited amount of information relating to the safety of NRT in pregnancy. There is no indication of significant harmful effect to the foetus associated with NRT, however, the finding that the NRT patch may deliver more nicotine than would be delivered by smoking is of concern.

Summary of findings from studies investigating specific aspects of the safety profile of NRT

Overall, the aspects of safety related to NRT use as explored in clinical studies indicate that nicotine acquired from NRT has similar effects to those from smoking, though generally these effects are reduced. There is no evidence that NRT acquired nicotine has any greater effects than an individual would be exposed to whilst smoking.

4.2.1.4 Surveillance studies of NRT

A major flaw with safety data collected from clinical trials of any sort is that the patient populations included in those trials are selected, particularly with regard to any known

increased risk of suffering an adverse event with the given intervention. Such a selected population may not accurately reflect the patient population prescribed the drug after its licensing by the regulatory authorities. Most countries have monitoring schemes, which require companies and physicians to report significant adverse events: usually those with potentially serious consequences for the patient or those not identified by pre-licensing clinical studies.

Description of surveillance studies of NRT

Three published reports of surveillance data for NRT have been identified.[93, 95, 117] Two unpublished reports were also identified,[96, 97] but for reasons of commercial confidentiality are not included in this review.

Quality of surveillance studies of NRT

The quality of surveillance data is difficult to assess. All surveillance studies included in this section were based on appropriate populations, with the source clearly stated. For all studies it was unclear whether specific data had been excluded.

Adverse events data from surveillance studies of NRT

Two of the published reports (considered one reference for the purpose of this review) summarise and compare the adverse events for the NRT patch and gum (Polacrilex resin) reported to the FDA Spontaneous Reporting System.[93, 117] A total of n=3848 adverse events were reported with the NRT patch (11.8 adverse events per million treated participants) and n=1281 (12.3 per million treated participants) the gum. The data for specific adverse events are summarised in Table 11 below.

Table 11. Adverse events reported to FDA SRS[93]

Adverse event	NRT Patch		NRT gum	
	Number reported	Number per million treated	Number reported	Number per million treated
Dermatologic (local or general)	1533	130	39	3.2
Addiction or dependence	24	2	475	39
Gastrointestinal, hiccups	522	44	163	13
Oral problems	141	12	289	23
Withdrawal, no effect, headache	442	38	156	13
Nervous system, CNS	384	33	75	6.1
Sleep and dream disturbance	416	35	17	1.4

All classes of adverse event were more common with the patch than with the gum except for oral problems which were more common with gum. The paper reported that in addition to the adverse events reported in the table, there were 18 times more allergy-related events with the patch and that overall, the patch is eight-times more likely to be associated with an adverse event than the gum.

The UK Medicines Control Agency (MCA) yellow card adverse events monitoring scheme for the period from 1980 onwards has received a total of 620 reports describing a total of 1091 reactions associated with the administration of all licensed formulations of NRT.[95] These include 13 fatalities (classified as seven cardiovascular, three cerebrovascular, one neurological, one congenital and one stillbirth). Non-fatal adverse events reported with NRT are: n=139 gastrointestinal, n=79 cardiovascular, n=60 abnormal dreams or nightmares, n=42 musculoskeletal, n=16 allergies, n=11 cerebrovascular, and n=8 congenital abnormalities.

In addition, a publication from the Netherlands Centre for Monitoring of Adverse Reactions to Drugs states that a total of 220 reports of drug-induced chest pain or myocardial infarction have been received over a 20 year period (1975-1994).[94] Of these, a total of nine (five MI and four chest pain) have been associated with NRT (eight with patches and one with gum). Nicotine was the second most frequently reported drug associated with MI or chest pain. The proportion of drug-induced MI and chest pain attributed to nicotine was 4.1%.

Summary of findings of surveillance studies of NRT

The incidence of adverse events reported in association with all types of NRT is low. The majority of the data pertain to patch or gum and reflect the concern for cardiovascular safety with NRT already identified from experience with tobacco-derived nicotine, as well as the adverse effects of the individual types of NRT identified in clinical trials.

4.2.1.5 Case report and case series studies of NRT

Description of case report and case series studies of NRT

A total of 17 case reports or case series were identified. All case reports or case series reporting an adverse event in association with NRT are listed in Appendix 9.9.

Quality of case report and case series studies of NRT

Not applicable

Adverse events results from case report and case series studies of NRT

Five case reports were of occurrences of suspected allergy to nicotine patches, characterised by rashes and swelling. Two cases reported myocardial infarctions, one in a patient who had smoked whilst wearing a nicotine patch and the other in a patient who had

suffered previous chest trauma. In another case report, a patient who had ingested large amounts of nicotine gum suffered from palpitations. Another reported a stroke following patch application. Other adverse events reported include: a worsening of myasthenia gravis following nicotine patch application; hiccups following nicotine gum use; increased cholesterol levels after taking nicotine gum; exacerbation of a duodenal ulcer; faintness, agitation and palpitations following nicotine patch application; suspected nicotine psychosis; migraine headaches; and an anaphylactic reaction following a wasp sting at the patch site.

Summary of findings of case report and case series studies of NRT

The majority of adverse events reported as case reports of case series were cardiovascular or rashes with, or without itchiness. No new areas of concern have been identified.

4.2.1.6 Overall summary of adverse events data for NRT (all study designs)

Table 12 presents an overall summary of the adverse events and safety data for NRT.

Table 12. Summary of adverse events and safety data for NRT

	Systematic reviews	Studies of incidence	Surveillance studies
Common adverse events	*Gum*: hiccups, gastrointestinal disturbances, jaw pain, and orodental problems. Patch: skin sensitivity and irritation, respiratory symptoms other than asthma or bronchitis, sleep disturbances, and alteration of mood. Inhaler: throat irritation, coughing, and oral burning. Nasal spray: nasal irritation and runny nose. *Nicotine sublingual tablets*: hiccups, burning and smarting sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers.	*Gum*: mouth irritation, dental problems, mouth ulcers, indigestion, hiccups, throat irritation, jaw ache/problems, nausea, belching. *Patch*: sleep disturbance, skin reaction, tight chest, racing heart, light-headedness; nausea; vomiting; headache. Nasal spray: headache, burning sensation in nose, throat or unspecified areas, watering eyes, nasal irritation, throat irritation , sneezing , runny nose, cough, and awakening during the night or early awakening	Given the nature of the monitoring schemes, from which these data are derived, it is likely that many reports are of a serious nature. Usually there is no differentiation between AEs and serious AEs. *Patch*: dermatologic (local or general), gastrointestinal, nausea, vomiting, hiccups, withdrawal, no effect, headache, nervous system, CNS, sleep and dream disturbance, dizziness. gum: addiction or dependence, oral problems, gastrointestinal, hiccups, withdrawal, no effect, headache.
Serious Adverse events	None that were more common with NRT than with placebo or smoking	*Patch*: serious cutaneous reactions, serious sleep problems, increased severity of atherosclerotic cardiovascular disease. *Nasal spray*: Stroke	All NRT defined as serious: fatalities (cardiovascular, cerebrovascular, neurological, congenital and stillbirth). Non-fatal adverse events reported with NRT are gastrointestinal, cardiovascular, abnormal dreams or nightmares, musculoskeletal, allergies, cerebrovascular, congenital abnormalities.
General points			All classes of adverse event more common with patch than with gum except for oral problems which were more common with gum. In addition to the adverse events reported in the table there were 18 times more allergy-related events. Overall the patch is eight times more likely to be associated with and adverse event than the gum.
Comments on quality/ validity	Limited information for one[24] and one[52] had limited searching	Generally limited quality, particularly for sample size, accountability and description of statistical methods	good surveillance studies, but inherently of limited quality
Safety issues:			
Cardiovascular	Overall the results indicate that there are no significant adverse cardiovascular effects of NRT in healthy adults, either in terms of the effect on blood pressure or conduction. The results of RCTs and other studies do not indicate any short-term adverse effects of NRT in patients with CAD.		
Blood lipid profile	NRT may inhibit the normalisation of the lipid profile that usually occurs upon smoking cessation.		
Endothelial dysfunction	The effects of NRT on endothelial dysfunction appear to reflect those of nicotine acquired through smoking		
Body weight	Individuals who attempt smoking cessation with the aid of NRT may not gain as much weight in the short term as those who do not use NRT, but after one year there is no effect of NRT on body weight.		
Abuse potential	Most individuals are able to stop using NRT at the end of treatment without discomfort, and there are no major differences between the various forms of NRT. Stopping use of NRT (gum) is not greatly eased by gradual reduction of use, rather than abrupt withdrawal. Overall abuse potential is low. Some surveillance data suggest that gum may have the greatest potential		
Use in pregnancy	There is only a very limited amount of information relating to the safety of NRT in pregnancy. No indication of significant harmful effect to the foetus associated with NRT, however, of concern is the finding that NRT patch may deliver more nicotine than would be delivered by smoking.		

4.2.2 Adverse events and safety of bupropion

Although the purpose of this systematic review was to investigate the adverse event profile of bupropion SR, systematic reviews and studies of both bupropion IR as well as SR were considered. Therefore within this section the term bupropion will be used unless specifically referring to bupropion SR or bupropion IR when the specific term will be used as appropriate.

Two systematic reviews,[13, 40] and 60 individual studies (see Table 13 for reference breakdown) were identified for inclusion in the review. The individual studies consisted of seven RCTs, one non-RCT, 11 uncontrolled studies (including two short-term cohort studies and three retrospective poolings of data), one survey, four surveillance studies (one unpublished[97]), and 36 case reports or case series. Within the individual studies (irrespective of design) a total of five studies whose primary objective was to investigate the incidence of adverse events, 14 described investigations related to some specific aspect of the safety profile of bupropion, such as its effect on cardiovascular function and one case report related to the safety of bupropion in pregnancy. Two of these studies (an uncontrolled retrospective pooling of data and a surveillence study) are unpublished and will not be discussed further.[97]

Table 13. Summary of published references included for adverse events and safety of bupropion

	Objective of or Type of Study					
Design	**Incidence of AEs**	**Investigating specific aspects of the safety profile**	**Pregnancy**	**Surveillance**	**Individual Cases of AEs**	**TOTAL**
RCT		**n=7** 120 121 122 123 124 125 126				**n=7** 120 121 122 123 124 125 126
Non-RCT		**n=1** 127				**n=1** 128
Uncontrolled	**n=6** 129 130 131 132 133 97	**n=5** 134 135 136 137 138				**n=11** 129 130 131 132 133 97 134 135 136 137 138
Case control						**n=0**
Survey		**n=1** 139				**n=1** 139
Surveillance				**N=4** 140 141 95 97		**n=4** 140 141 95 97
Case reports or series			**n=1**[142]		**N=35** 143-177	**n=36** 178 143-177
TOTAL	**n=6** 129 130 131 132 133 97	**n=14** 120 121 122 123 124 125 126 128 134 135 136 137 138	**n=1** 178	**N=4** 140 141 95 97	**n=35** 143-153, 155-157, 159-175	**n=60** 120 121 122 123 124 125 126 128 129 130 131 132 133 97 134 135 136 137 138 139 140 141 95

						97 178 143-153, 155-157, 159-175
Note reference [130] also published as [179]. Also [142] included in [178]. Reference [97] refers to company submission not just a single study, therefore may appear in more than one section.						

4.2.2.1 Systematic reviews of bupropion

Description of systematic reviews of bupropion

Two systematic reviews containing information pertinent to the adverse effects and safety profile of bupropion were identified.[13, 40] Both included only studies involving bupropion SR. One review, a Cochrane Review, only included RCTs and was primarily a review of the effectiveness of bupropion SR.[40] The other systematic review included the same RCTs as the Cochrane Review, but also included additional studies (uncontrolled studies and case reports) relating to the safety and adverse event profile of bupropion SR.[13] Details of these systematic reviews are given in Appendix 9.7.2.6.

Quality of systematic reviews of bupropion

The quality of the Cochrane Review has been previously discussed in section 4.1.2.1.[40] In terms of adverse event and safety data it summarised briefly only those adverse events reported in RCTs in which bupropion SR was used for smoking cessation.

The other systematic review was based on literature searches of Medline, Embase and Adis Base (a proprietary database of Adis International).[13] Additional references were identified from the reference list of published articles. Validity of included studies was not formally checked, although the inclusion criteria stated that large, well-controlled trials with appropriate statistical methodology were preferred. Individual study details were presented briefly and the adverse event data were pooled appropriately in a narrative synthesis.

Adverse events data from systematic reviews of bupropion

Of the five RCTs included in both systematic reviews (see list in Appendix 9.12) two did not report adverse events data. The adverse events identified in the systematic reviews were rash and pruritus (sometimes associated with shortness of breath and tightness of chest); irritability; restlessness; anger; anxiety and craving; insomnia; dry mouth; headache; tremor; urticaria. There were no reports of seizure in any of the studies included in the systematic reviews. Serious adverse events reported included three cases of serious rash and pruritus, one of which was associated with shortness of breath and tightening of the chest. All had full resolution of symptoms. In addition there was one case of extreme irritability, anger, restlessness, anxiety and craving, which occurred in a man who had given up smoking.

The incidence of withdrawals due to adverse events reported in the three RCTs that provided data are described by individual study. For the first study, 11.9% in the bupropion SR group compared with 3.8% in the placebo, 6.6% in the nicotine patch, and 11.4% in the bupropion SR plus patch group. For the second study 8% in the bupropion SR (300 mg) group, 6% in the bupropion SR (100 mg) and 5% in the bupropion SR (150 mg), compared with 5% in the placebo group. In the third study in which participants received treatment for one year rather than a few weeks, there were 24/214 (11.2%) discontinuations in the bupropion SR group due to adverse events compared with 17/215 (7.9%) in the placebo group. Adverse events commonly associated with withdrawal were: rash, urticaria, insomnia, headache, dry mouth, and tremor.

The only adverse events that were statistically significantly more common with bupropion SR (100 or 300 mg/day) than with placebo were insomnia (34.6% and 42.4% compared with 20%) and dry mouth (12.8% and 10.7% compared with 4.5%).

There is almost no information from these reviews regarding possible cardiovascular effects of bupropion SR and no evidence relating to treatment emergent hypertension.

The incidence of depression associated with bupropion SR use for smoking cessation has been measured as 0.25% (1/406 participants treated for 7-weeks) and 1.4% from a 45-week treatment to-prevent-relapse study.

Treatment with bupropion SR 300 mg/day for a period of 8 weeks in participants with depression was associated with a seizure rate of 0.06% according to survival analysis. This was considerably less than that reported for bupropion IR (0.36%). The lack of a direct comparison between these two formulations of bupropion must be borne in mind.

The systematic reviews indicate that bupropion SR appears to have a low propensity for sexual adverse events in patients with depression.

Serum sickness-like reactions, rhabdomyolysis, possible transient ischaemic attack and increased libido with spontaneous orgasm have been described in case reports with bupropion SR 150 to 300 mg/day.

Summary of findings from systematic reviews of bupropion

The amount of information on adverse events reported in the systematic reviews is limited due to the small number of RCT studies of bupropion SR in smoking cessation. Furthermore,

the populations studied and included in these systematic reviews were ones that excluded all patients at risk of known adverse events of bupropion SR.

4.2.2.2 Studies whose primary objective was to investigate the incidence of adverse events with bupropion

Description of studies whose primary objective was to investigate the incidence of adverse events with bupropion

Three prospective uncontrolled studies that investigated primarily the incidence of adverse events with bupropion were identified.[129, 132, 133] Two were uncontrolled cohort studies[132, 133] and one was a small uncontrolled study.[129] In addition, two reports of data pooled from collections of clinical trials have been identified.[130, 131] It should be noted that[130] is also published as.[179] One of these included all participants enrolled in the clinical trials program of bupropion IR from 1970 to 1981 as reported by Wellcome Laboratories.[130] Another included all participants known to have been treated with bupropion IR prior to its receiving marketing authorisation.[131] The clinical data included in this study were made available by Burroughs Wellcome and included the total number of participants exposed to bupropion and include all reports of seizure to the company (which the authors are confident includes all actual seizures).

Quality of studies whose primary objective was to investigate the incidence of adverse events with bupropion

Of the prospective studies,[129, 132, 133] all three were conducted in appropriate populations and their aims were clearly stated. Follow-up, although long, could possibly have been longer given the uncertainty of long-term effects. For two studies it was not clear that the study design[133] [129] was appropriate and in one study the sample size did not appear to be appropriate.[129] The validity of measures was unclear in two studies[133] [129] and suitability of outcome measures was unclear in one study.[132] Patient accountability was unclear in one study[132] and the statistical methods were not clearly described in a further two studies.[133] [129] The two reports of retrospective pooling of data[130, 131] both included appropriate populations and had adequate follow-up. For both studies the aims were clearly stated and the study design, validity of measurements and choice of outcome were appropriate. In both the statistical methods used appeared suitable.

Adverse events data from studies whose primary objective was to investigate the incidence of adverse events with bupropion

Of the three prospective uncontrolled studies,[129, 132, 133] one study was small, including only 22 participants and therefore of extremely limited utility in determining the safety of bupropion.[129] Further details are given in Appendix 9.7.

A multicentre, unblinded, uncontrolled study investigated the adverse events associated with eight weeks of treatment with bupropion IR 225-450 mg/day in 3279 adult patients diagnosed as suffering from depression for which antidepressant treatment was clinically appropriate.[133] Of these patients 1942 were taking a daily dose of 450 mg. The study reported a total of 13 grand mal seizures: eight had occurred during the eight-week treatment phase and a further five during a continuation of treatment. The calculated observed seizure rate during 56 days treatment phase was 0.24% with upper one-sided 95% CI was 0.38%. Observed seizure rate for the whole study was 0.40% with upper one-sided 95% CI of 0.58%. The survival analysis performed on participants who took 300-450 mg/day (n=2708) showed a cumulative rate of 0.36% in the 56 day treatment period, with upper one-sided 95% CI of 0.57%.

Unfortunately the report of this study gave only very limited details of the other adverse events reported. A total of 84 other adverse events that were life threatening or required hospitalisation are reported: n=56 psychiatric, n=22 unrelated to drug (e.g. hospitalisation for road traffic accident), n=6 possibly bupropion IR related (drug discontinued).

A second multicentre, unblinded, uncontrolled study investigated the adverse events associated with bupropion SR.[132] This study utilised bupropion SR (titrated from 50 to 150 mg b.i.d) for a period of eight weeks, which could then be extended for up to one year and included a total of 3100 adult patients with DSM-III-R diagnosis of depression. A total of 2057 (66%) patients completed the eight-week acute phase and 1577 (77%) of these entered the continuation phase.

Three participants experienced a seizure; two within the first eight weeks, giving an observed incidence rate of 0.06% (upper one-side CI: 0.14%). The observed seizure rate for the whole study period (1yr) was 0.10% (upper one-side CI: 0.19%). In participants who consumed therapeutic dose of bupropion SR (n=2958) the survival analysis yielded a cumulative seizure rate of 0.08% (upper one-sided CI: 0.18%) for the acute phase and 0.15% (upper one-sided 95% CI: 0.30%) for the whole follow-up. There were some predisposing factors in two of the three cases: alcohol withdrawal 11yrs previously; and loss of consciousness in a motor accident and possible alcohol abuse. In addition, the third participant had a history of alcohol abuse, although no evidence of recent alcohol use.

It was also reported for this study that 50 out of 3100 participants reported 54 serious adverse events. These included suicide attempt or overdose (nine participants), accidental injury (four participants), myocardial infarction (three participants all who had pre-existing cardiovascular pathology). There were also six deaths (three suicides, two cardiac complications, one homicide). The events precipitating these deaths were not considered related to bupropion SR. Overall 84% of participants who received at least one dose of bupropion SR did not experience an adverse event that significantly interfered with functioning.

The first retrospective pooling of adverse event data included a total of 1153 patients diagnosed with depression and 157 healthy volunteers.[130] All participants had demonstrated normal and/or clinically acceptable values for physical examinations, vital signs, clinical laboratory test (haematology, clinical chemistry, urinalysis), and EEG. Concomitant medication, with the exception of chloral hydrate had been prohibited except in three studies where antipsychotics were also permitted. The duration of treatment had been four to 13 weeks (averages across studies) and the dosage regimens of bupropion IR were 15-1200 mg/day (most common 300-450 mg/day).

A total of 14.4% of participants withdrew due to adverse events. The adverse events most commonly resulting in withdrawal are presented in Table 14.

Table 14. Adverse events leading to withdrawal from bupropion IR

Adverse event	Percentage of pts wthdrawing due to AE
Excitement/agitation	9.1%
Anticholinergic	5.4%
Miscellaneous	4.6%
Motor disturbance	4.5%
Psychological problems	3.9%
Dermatologic	3.0%
Nausea/vomiting	2.7%
Drowsiness	2.6%
Weight loss	2.4%
Headache/nasal congestion	2.4%
Thinking difficulties	2.1%
NB participants may have withdrawn due to more than one event. Only adverse events with at least >2% occurrence are included but have 1.8 and 1.4% in the table)	

Although the majority of participants had no change in the EEG during treatment, 6.2% who had normal findings at baseline were found to have abnormal ones after bupropion IR. Major motor seizures were reported by two healthy volunteers and eight patients. Two volunteers had seizures after two or four days of consecutive 800 mg single doses after at least 40 days of treatment at lower doses (up to 550 mg/day). Of the eight patients who had seizures, one had a history and one a possible history of seizure. The dose at which seizures occurred

ranged from 600 mg to 900 mg/day except in one patient, with history of seizure, who took 450 mg/day.

The second retrospective pooling of data looked only at the cases of seizure reported with bupropion IR.[131] The study included all participants known to have been treated with bupropion IR prior to its receiving marketing authorisation. It included a total of 4262 participants (4097 patients suffering from depression and 165 healthy volunteers) and it is likely that all cases of bupropion IR-associated seizure will have been included in this analysis. Clearly this population overlaps with that in the previous study.[130] A total of 37/4262 reported a seizure, giving a crude overall incidence of 0.87%. Nineteen seizures occurred at doses above 450 mg/day. The incidence associated with lower doses is 0.35%. The cumulative risk over 2 years is 0.48% up to day 720, if only doses of less than 450 mg/day are considered. At all doses the risk is 1% by day 180 increasing to 1.74% by day 720. The dose at which seizure occurred ranged from 100 mg to 9000 mg. The length of time participants received the dose of bupropion IR at the dose at which the seizure occurred ranged from 1 to 281 days (mean 8 days), with 21 cases being on that dose for 15 days or less. For the 21 cases for whom the information was available, 77.3% of seizures occurred within 240 minutes of a dose of bupropion. Eleven of 1802 (0.61%) males suffered seizures compared with 23/2457 (0.93%) females, but this difference between genders was not statistically significant. There was no association between seizure risk and age. Fourteen participants were considered to have predisposing factors: four had a history of seizure (one plus head trauma); one had metastatic brain carcinoma; one was undergoing alcohol withdrawal; one had head trauma; five were receiving concomitant medication known to lower the seizure threshold; and for two the predisposing factors were not stated.

With regards to the data on all adverse events, only those that resulted in withdrawal of treatment were included in the summary and furthermore, given the relatively small size of database (n=1153 participants), the cut off of 2% for inclusion in this summary must mean many events were not included in this publication.

The seizure rate from retrospective study is much higher than that from prospective ones. These data support the findings from the prospective studies that the risk of seizure with bupropion is particularly associated with doses of 450 mg/day and above, and that the risk increases with duration of treatment.

Summary of findings from studies whose primary objective was to investigate the incidence of adverse events with bupropion

For bupropion SR the common adverse leading to withdrawal were skin disorders (mainly rash), insomnia, tremor, headache, dry mouth and anxiety. For bupropion IR the common adverse events leading to withdrawal were excitement/agitation, anticholinergic, miscellaneous, motor disturbance, psychological problems, dermatologic, nausea/vomiting, drowsiness, weight loss, headache/nasal congestion, thinking difficulties, dizziness, tachycardia/palpitations.

Calculated observed seizure rate with IR during 56 days treatment phase was 0.24% with upper one-sided 95% CI of 0.38%. Observed seizure rate for whole study duration 0.40% with upper one-sided 95% CI of 0.58% compared to 0.06% (upper one-side CI 0.14%) (956 days) and 0.10% (upper one-side CI 0.19%) (one year) with SR. In addition to seizures, other adverse events that were life threatening or required hospitalisation with bupropion SR were: psychiatric, unrelated to drug (e.g. hospitalisation for road traffic accident). Serious AEs included: suicide attempt or overdose, accidental injury, myocardial infarction (all who had pre-existing cardiovascular pathology), and six deaths.

4.2.2.3 Studies investigating specific aspects of the safety profile of bupropion

Description of studies investigating specific aspects of the safety profile of bupropion

These 14 studies address specific investigations conducted in relation to the adverse events and safety profile of bupropion concentrated on the possible cardiovascular effects of bupropion, its possible effects on sexual function, and its effect on weight. [120-126, 128, 134-139] It should be noted that all studies relating to bupropion-associated seizures have been included in the previous section (4.2.2.2).

Three of the seven RCTs were double-blind,[120 121 124] two[122, 123] were unblinded and for two studies the status of blinding was unclear.[125, 126] One study failed to achieve at least 80% completion[124] and one was unclear regarding the number of patients withdrawn[126] and three were unclear for both of these.[120, 121, 123] None of the studies were clearly analysed according to intention-to-treat principles. Of the five uncontrolled studies, none were clear regarding the adequacy of the sample size. Three were unclear for accountability.[134, 135, 138] Two studies described the statistical methods poorly[134, 135] and for two studies the appropriateness of the statistical methods was unclear.[135, 138] In two studies the appropriateness of the study design was unclear.[135, 136] One study[139] was a small survey, with all its inherent unreliability.

Adverse events data from studies investigating specific aspects of the safety profile of bupropion

a) Effects of bupropion on cardiovascular function

A total of six studies that examined the possible effects of bupropion on cardiovascular function were identified.[120-122, 127, 134, 135] Three of these studies were RCTs,[120-122] one was a non-randomised controlled trial[127] and two were uncontrolled studies.[134, 135] All were conducted in populations of patients being treated for depression.

The three RCTs all compared bupropion IR with another antidepressant. Two of the RCTs were double-blind, parallel group comparisons and included 135 and 115 participants respectively, who had no cardiovascular disorder.[120, 121] The third RCT was a very small (10 participants), unblinded, crossover comparison in patients with a history of congestive heart failure (CHF).[122]

In the two RCTs in participants without cardiovascular disease[120, 121] no effects on sinus heart rate or cardiac conduction were reported. Neither study reported symptomatic orthostatic hypotension, however in one study[120] 8/55 patients had orthostatic changes (defined as a drop of 20 mm Hg after 1 min standing), which was at least 20 mm Hg greater than the orthostatic drop at baseline. In the small RCT of patients with CHF [122] bupropion IR had little effect on cardiovascular function, with no real changes from baseline in ejection fraction, end diastolic volume, end systolic volume, peak systolic pressure: end systolic volume ratio, or supine systolic blood pressure. The mean orthostatic fall in blood pressure on bupropion IR was 2 mm Hg.

The non-randomised controlled trial, in which 23 patients were treated with bupropion IR 300-750 mg/day reported no significant changes in any of the ECG parameters measured.[127] The two uncontrolled studies[134, 135] also found no evidence of adverse cardiovascular effects of bupropion IR. Further details are given in Appendix 9.7.

Summary of effects of bupropion on cardiovascular function

Together, with particular emphasis on the findings of the two double-blind RCTs, these studies indicate that bupropion does not have any clinically significant adverse effects on cardiac and cardiovascular function.

b) Effects of bupropion on sexual function

A total of six studies were identified that investigated the effects of bupropion on sexual function.[123-126, 137-139] Four of these studies were RCTs: three conducted in patients suffering from depression [123, 124, 126] and one in healthy volunteers.[125] Of the non-RCTs two were uncontrolled studies[137, 138] and one was a survey.[139] Two of these were conducted in patients suffering from depression[137, 139] and one in non-depressed men with diabetes.[139] Further details of all the following studies are given in Appendix 9.7.

Two of the RCTs were double-blind, parallel group studies that compared bupropion SR with sertraline (an anti-depressive drug).[123, 124] They found that the proportion of bupropion SR patients reporting various forms of sexual dysfunction was statistically significantly lower than in the other treatment group. The third RCT was a double-blind, placebo-controlled, crossover study of the effects of two weeks of therapy with bupropion SR conducted in 13 healthy volunteers.[125] Sexual function was unchanged during the placebo or bupropion SR phase of the study.

A small uncontrolled study included patients who had experienced sexual dysfunction when treated with other antidepressants.[137] This study found that of the 28 patients with sexual dysfunction while on other antidepressants, 24 improved completely over a 1- to 4-month period on bupropion IR.

Another small uncontrolled study assessed the effect of bupropion IR on sexual desire and erectile function in 15 men aged 21 to 60 years, with erectile dysfunction due to their diabetes.[137] There was no evidence from this study that bupropion IR worsened or interfered with sexual desire or erectile functioning.

A survey of psychiatric outpatients from a single clinic found that of the 22 patients who were receiving bupropion IR, none reported decreases in sexual function over baseline.[139] In contrast some patients reported significant increases in sexual function over baseline, in terms of libido, arousal, duration and intensity of orgasm, whereas those receiving other antidepressants (fluoxetine, paroxetine, or sertraline), reported detrimental effects in terms of sexual functioning. The very small population sample size severely limits the reliability of these findings.

Summary of effects of bupropion on sexual function

The data from RCTs indicates that bupropion is less likely to cause sexual dysfunction than other antidepressants. The one very small RCT in healthy volunteers indicates no adverse sexual effects of bupropion SR; a finding particularly relevant to the use of bupropion SR for

smoking cessation. The evidence from the small uncontrolled studies and survey is supportive of these findings.

c) Effect of bupropion on body weight change

One small uncontrolled study was identified that investigated the effect of bupropion IR on body weight.[136] A total of 58 outpatients diagnosed with a nonpsychotic depressive disorder, who poorly tolerated tricyclic antidepressants (many specifically due to weight gain) were treated with bupropion IR 50-600 mg/day (most common 300-450 mg/day) for up to one year (mean 9 months). After 3, 6, 9 or 12 months on bupropion IR therapy (mean 9 months) the mean terminal weight change was 4.8llbs for men and 8.0 lbs for women. Overall, 42 patients (72%) lost weight (35 patients lost more than 5lbs) and 24% gained weight (seven patients gained more than 5lbs), with 4% no changes. Changes in weight corresponded poorly to patients' reports of appetite suppression or increase. This was a small study, with limited details of participants, that would have been better conducted as an RCT. The applicability these findings to participants using bupropion SR for smoking cessation is questionable.

d) Studies related to the use of bupropion during pregnancy or lactation

Pre-clinical data have not established the safety of bupropion in pregnancy (SPC for Zyban®)[180] and therefore clinical trials have not been conducted. Only one published reference has been identified regarding the use of bupropion by breast feeding mothers and this related to just a single individual.[178] This female patient was receiving bupropion 300 mg/day. The infant was 14 months (60 weeks) old and was receiving two breast feeds per day to supplement other food. Maternal serum concentrations of bupropion, hydroxybupropion and threohydroxybupropion were 72 ng/ml, 59 ng/ml and 282 ng/ml respectively, indicating that bupropion and its metabolites are secreted into the breast milk. The respective infant serum levels were <5 ng/ml, <20 ng/ml, and <20 ng/ml. This evidence from a single individual indicates that bupropion passes into the breast milk. There is no evidence of the safety of bupropion in pregnancy or breast feeding.

Summary of findings from studies investigating specific aspects of the safety profile of bupropion

The available studies indicate that bupropion does not have any clinically significant adverse effects on cardiac and cardiovascular function. The data from RCTs indicates that bupropion is less likely to cause sexual dysfunction than other antidepressants. The one very small RCT in healthy volunteers indicates no adverse sexual effects of bupropion SR; a finding particularly relevant to the use of bupropion SR for smoking cessation. The evidence from

the small uncontrolled studies and a survey is supportive of these findings. There is very limited evidence that smokers abstaining with aid of bupropion SR do not gain weight. There is no evidence to support the removal of the contra-indication to bupropion SR in pregnancy or breast feeding.

4.2.2.4 Surveillance studies of bupropion

The reason for including this type of study has been discussed in section 4.2.1.4

Description of surveillance studies of bupropion

Three published sources of surveillance data relating to bupropion SR were identified.[95, 140, 141] All three studies report data from country-specific safety monitoring databases: the Medicines Control Agency (MCA)[95], Australian Adverse Drug Reaction Advisory Committee (ADRAC)[140] and the Canadian Adverse Drug Reaction Monitoring Program (CADR),[141]).

Quality of surveillance studies of bupropion

The quality of data from the surveillance studies is difficult to assess. Theoretically the databases derive their information from the total population of treated individuals. There appear to be differences in policy regarding publication of reports of adverse drug reactions, with the larger databases publishing only information on the most common adverse events reported to them. All of the databases appear to include all serious or unexpected adverse events reported for bupropion SR since its launch in that given country, with no obvious exclusions or omissions which may affect the findings.

Adverse events data from surveillance studies of bupropion

The published data are summarised in Table 15.

Table 15. Number of adverse reactions reported for bupropion SR (Zyban®)

Adverse Event	MCA	ADRAC	C ADR Monitoring Program
Total number of individuals exposed to drug	390,000 (June 2000 to May 2001)	Not reported (November 2000 to May 2001)	Not reported (monitoring period Aug 18 1998 to Dec 1st 1998)
Total number of individuals with adverse reactions			48
Total number of adverse reactions	5593	780	144
Urticaria	761	167	7
Insomnia	761	78	5
Rashes	724	86	11
Headache	537	68	1
Dizziness	534	78	5
Nausea	489	87	4
Angiodema	348	62	2
Depression	345	45	
Tremor	279	57	6
Pruritus	283	46	9
Anxiety	232	50	5
Chest pain	238	54	
Dry mouth	189		
Dyspnoea	184	38	3
Palpitations	174		2
Agitation	160	58	
Vomiting	161	30	3
Increased sweating	145	33	
Chest tightness	134		
Constipation	133		
Arthralgia	128		
Abdominal pain	119		
Seizures	118*	48[#]	3[&]
Malaise	118**		2
Death	37***	9[##]	
Serum Sickness	0	33	1[&&]
Paraesthesia/hypoaesthesia/ dysaesthesia	0	40	5
Suicidal ideation			3
Hallucination			3
Stupor			3
Dysphagia			3
Dyspepsia			3
Paralysis			2
Abnormal coordination			2
Hyperkinesia			2
Tachycardia			2
Oedema			7
Allergic reaction			2
Fatigue			2
	(*approx. ½ participants had either past history of seizures and/or risk factors for their occurrence) Estimated incidence of dose-related risk of seizure: 0.1% (1/1000)	[#]classed as convulsions/twitching [##]ADRAC is satisfied to data that bupropion has not emerged as a cause of unexpected deaths.	[&]One case convulsions only [&&]Stevens-Johnsons syndrome
	(**sum of reports exceeds total no)		
	(***in 9 cases, participants were not taking bupropion at time of death)		

In addition to those listed in the table the following adverse events were each reported once to the Canadian Adverse Drug Reaction Monitoring Program: dyskinesia, dysaesthesia, vertigo, speech disorder, headache, convulsions, parasthesia; Stevens-Johnson syndrome,

rash maculo-papular; skin discolouration; fever, Bells Palsy aggravated, aesthenia, sensation of warmth; cold extremities, oedema peripheral, mouth oedema, pharynx oedema; aggressive reaction, anorexia, paranoia, confusion, depression, nervousness, concentration impaired, agitation; flushing, myocardial infarction, angina pectoris; dyspepsia; hyperventilation, rhinitis; arthralgia, arthropathy , myalgia; mydriasis, photophobia, earache, epistaxis.

Summary of findings from surveillance studies of bupropion

It is clearly difficult to interpret the data reported in these studies, especially given that the size of the populations treated is either not given or is at best an estimate. Furthermore, there appear to be differences in policy regarding publication of reports of adverse drug reactions, with the larger databases publishing only information on the most common adverse events reported to them. The adverse events reported most commonly are: Urticaria, insomnia, rashes, headache, dizziness, nausea, angiodema, tremor, depression, pruritus, anxiety, chest pain, dry mouth, dyspnoea, palpitations, agitation, vomiting, increased sweating, arthralgia, chest tightness, constipation, death, abdominal pain, seizures, malaise, serum sickness, paraesthesia/ hypoaesthesia/ dysaesthesia.

4.2.2.5 Case reports and case series of bupropion

Description of case reports and case series of bupropion

Thirty-six case reports were included[143-153, 155-178]. All except one,[178] which is not a report of an adverse event but which describes the measurement of bupropion blood levels in maternal and nursing infant's blood, are summarised in Appendix 9.9.

Quality of case reports and case series of bupropion

Not applicable

Adverse events data from case report and case series studies of bupropion

Thirty-five case reports were included. There were two reports where the patient had taken an overdose of bupropion, and in each case the patient had suffered a seizure. Sixteen case reports reported that the patient had experienced either mania, episodes of psychoses, hallucinations, and delirium. The majority of these patients had co-existing psychiatric disorders (including bipolar disorder and major depression). Other adverse events reported in this area included impairment to nerve function, nightmares, catatonia, dykinesia and falling backwards. There were seven reports of serum sickness-like reaction and three cases where patients had experienced sexual dysfunction. One case reported on two females who had suffered disruption to their menstrual cycle whilst taking bupropion. Other

adverse events reported included: tinnitus; eosinophilia; transient ischaemic attacks; exacerbation of hepatitis, and; rhabdomyolysis.

Summary of findings from case report and case series studies of bupropion

The majority of adverse events reported as case reports or case series relate to psychiatric adverse effects of bupropion. Reports of serum-sickness-like reactions and rhabdomyolysis suggest possible areas for future vigilance.

4.2.2.6 Overall summary of adverse events data for bupropion (all study designs)

Table 16 presents an overall summary of adverse events/safety data for bupropion.

Table 16. Summary of adverse events and safety data for bupropion SR and IR

	Systematic reviews	Studies of incidence	Surveillance studies
Common adverse events	Rash and pruritus, irritability, insomnia; dry mouth; headache; tremor; urticaria, rash; urticaria; insomnia; headache; dry mouth; and tremor	*Bupropion SR*: Data on common adverse leading to withdrawal are unpublished. *Bupropion IR*: common adverse leading to withdrawal were excitement/agitation, anticholinergic, miscellaneous, motor disturbance, psychological problems, dermatologic, nausea/vomiting, drowsiness, weight loss, headache/nasal congestion, thinking difficulties, dizziness, tachycardia/palpitations.	Given the nature of the monitoring schemes from which these data are derived, it is likely that many reports are of a serious nature. Usually there is no diffferentiation between AEs and serious AEs. Urticaria, insomnia, rashes, headache, dizziness, nausea, angiodema, tremor, depression, pruritus, anxiety, chest pain, dry mouth, dyspnoea, palpitations, agitation, vomiting, increased sweating, arthralgia, chest tightness, constipation, death, abdominal pain, seizures, malaise, serum sickness, paraesthesia/ hypoaesthesia/ dysaesthesia.
Serious adverse events	Serious rash and pruritus, one of which was associated with shortness of breath and tightening of the chest. All had full resolution of symptoms. In addition there was one case of extreme irritability, anger, restlessness, anxiety and craving, which occurred in a man who had given up smoking.	*Bupropion SR*: in addition to seizures, other adverse events that were life threatening or required hospitalisation were: psychiatric, unrelated to drug (e.g. hospitalisation for road traffic accident), possibly bupropion related (drug discontinued). Serious AEs included: suicide attempt or overdose, accidental injury, myocardial infarction (all who had pre-existing cardiovascular pathology), 6 deaths.	
Seizures	Crude rate of 0.3% at 6 days with IR and 0.06 with SR.	Calculated observed seizure rate with IR during 56 days treatment phase was 0.24% with upper one-sided 95% CI of 0.38%. Observed seizure rate for whole study duration 0.40% with upper one-sided 95% CI of 0.58% compared to 0.06% (upper one-side CI 0.14%) 956 days and 0.10% (upper one-side CI 0.19%) (one year) with SR.	118 from base of 390,000 individuals exposed June 2000 to May 2001.
General points	The only adverse events statistically significantly more common with bupropion SR than with placebo were insomnia and dry mouth		
Comments on quality/ Validity	Limited information from one[40], the other was of good quality except for lack of individual study details[13]	Generally of limited quality, particularly relating to limited reporting of AEs other than seizures	Good quality surveillance studies
Safety issues			
Cardiovascular	The available studies indicate that bupropion does not have any clinically significant adverse effects on cardiac and cardiovascular function.		
Sexual dysfunction	The data from RCTs indicates that bupropion is less likely to cause sexual dysfunction than other antidepressants. The one very small RCT in healthy volunteers indicates no adverse sexual effects of bupropion SR; a finding particularly relevant to the use of bupropion SR for smoking cessation. The evidence from the small uncontrolled studies and survey is supportive of these findings.		
Body wt	Very limited evidence that smokers abstaining with aid of bupropion SR do not gain weight.		
Pregnancy	Contra-indicated		

5 ECONOMIC EVALUATION OF SMOKING CESSATION INTERVENTIONS

This section includes two sub-sections: a review of existing studies, and a model of the cost-effectiveness of smoking cessation interventions.

5.1 A REVIEW OF EXISTING STUDIES

Identified studies of the economic evaluation of smoking cessation interventions are presented in Appendix 9.10. These studies have been classified according to their relevance to this review.

- Six studies that estimated the cost-effectiveness of NRT in the UK setting are considered the most relevant.[22, 181-185]
- Several studies conducted in other countries which evaluated cost-effectiveness of NRT are considered relevant.[186-189]
- Two studies carried out a cost-benefit analysis of bupropion SR for smoking cessation.[190 191]
- Some studies about smoking cessation interventions provided useful information but they did not estimate the cost-effectiveness of NRT or bupropion SR separately.[192-194]
- One study in the United States assessed the impact of insurance coverage on the use of smoking cessation interventions.[195]

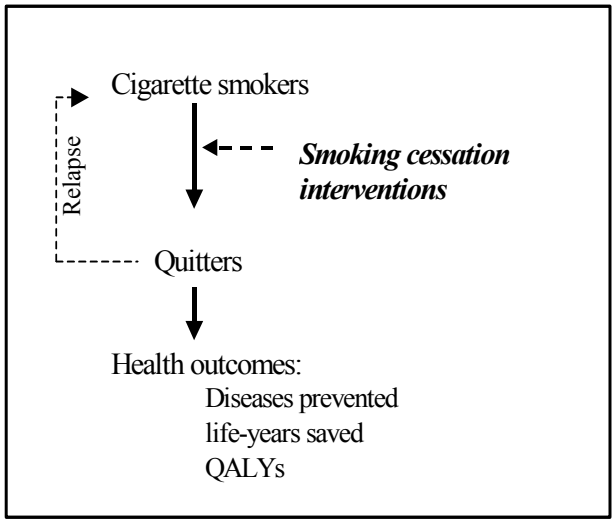
This review focuses on face-to-face interventions to the general population delivered by health care professionals, relying mainly on the first two groups of studies outlined above, and using the others as necessary for effectiveness estimates in modelling.

5.1.1 Estimating effectiveness in economic evaluation

Evaluation of effectiveness of smoking cessation interventions generally involves two stages (Figure 3):

- converting number of smokers to number of (short-term or long-term) quitters;
- and estimating health consequences of smoking cessation according to the number, age and gender of the quitters .

Figure 3. Two stage process for estimating effectiveness of smoking cessation interventions



5.1.2 From smokers to quitters

In economic evaluations, the quit rate is usually estimated according to the results of systematic reviews or meta-analyses of clinical trials but sometimes, results of an individual trial are used. Because of the relatively large amount of data from clinical trials, the estimated relative effect of NRT may be considered robust. However, few studies have compared bupropion SR against competing interventions.

The definition of 'quitters' is complicated by several factors. Assessment of smoking cessation may be based on self-report with or without biochemical validation. In clinical trials, the definition of smoking cessation has often been defined as continuous abstinence for 6-12 months. Since the duration of follow-up is generally up to 12 months in clinical trials, the long-term (lifetime) cessation has to be estimated based on limited data. The rate of lifetime relapse used in the existing studies of economic evaluation has ranged from 0% to 50% (see Appendix 9.10).

Questions exist as to whether the results of trials can be generalised to the whole smoker population. Smokers who participate in trials may be more motivated to stop smoking. If so, the quit rate in all groups (including the control group) would be higher than that when the

same interventions are applied to the whole smoker population. Use of relative (rather than absolute) effectiveness for the different interventions may ameliorate this problem.

The spontaneous (background or natural) quit rate must be included in estimating the net effect of smoking cessation interventions. In the existing economic evaluations, this ranges from 1% (most of the UK studies) to 8% per year. In one study, it is 1.5% (95% CI 1.2, 1.8%) based on data from the Office of National Statistics' General Household Survey in the UK.[185]

Side-effects due to smoking cessation interventions have not been incorporated in the existing economic evaluations. The assumption that there are no important side-effects associated with smoking cessation intervention may not be appropriate in the evaluation of some pharmacological products such as bupropion SR, but the rarity of side effects means that their exclusion is unlikely to have major impact.

5.1.3 From number of quitters to long-term health outcomes

Compared with estimating the number of quitters, it may be more difficult and problematic to estimate long-term health outcomes from the number of quitters. The long-term health outcomes following smoking cessation could be measured as the number of deaths prevented, life-years saved, or quality-adjusted life-years saved. The number of life-years saved is the most commonly used measure.

Life-years saved

The number of life-years saved is a more important outcome than the number of quitters. Use of life-years saved enables comparisons of the cost-effectiveness of smoking cessation interventions with other life saving healthcare interventions. However, the estimation of life-years saved after cessation is less accurate than numbers of quitters. The incremental life-years saved after cessation depend on many factors, such as the age and gender of quitters, number of cigarettes smoked, duration of smoking before cessation, and relapse rates. Methodological issues include the validity of data from observational studies, and whether and how much the life-years saved in the future should be discounted.

Three UK studies have used the PREVENT model[196] to estimate the impact of changes in smoking behaviour on specific diseases: lung cancer, coronary heart disease (CHD), and chronic obstructive pulmonary disease (COPD) (Appendix 9.10). In other studies, the difference in the total mortality between smoker and non-smokers or former smokers was used to estimate the life-years saved after cessation. For example, studies have used data

from Doll et al.'s cohort study of male doctors in England,[197] or data from the American Cancer Society's 25-state Cancer Prevention Study.[198]

According to the existing studies of economic evaluation, the average life-years saved per quitter range from 0.28[182] to 2.4,[183] depending on the model and discount rate used. The life years saved per quitter was about one year in Parrott et al., using the PREVENT model and an annual discount rate of 1.5%.[22] Without discounting, the number of life-years saved per quitter increases to 1.54.

By using life expectancy data from various sources and a discount rate of 3%, a US study estimates that the years of life saved per long-term quitter was 1.31 for men aged 25-29, 0.47 for men aged 65-69, 1.43 for women aged 25-29, and 1.41 for women aged 65-69.[186] The weighted average of life-years saved per quitter is 1.46. This study has used a relapse rate of 45% and the quitters are lifetime quitters who did not smoke again over the rest of their lives. It can be estimated that the number of life-years saved per quitter at 12 months is 0.8.

A recently developed model, the Health and Economic Consequences of Smoking (HECOS), has adopted an approach similar to the PREVENT model to estimate the life-years saved after smoking cessation.[184] The HECOS model estimates the morbidity and mortality associated with smoking related diseases, including chronic obstructive pulmonary disease, coronary heart disease, stroke, lung cancer, and low birth weight pregnancy. Despite the fact that the HECOS model does not discount long-term health benefits, it provides a relatively low value of 0.4 life-years saved per quitter.[184] In the HECOS model the duration of follow-up is up to 20 years, although gain in life-years may continue in quitters after 20 years. Consequently, the number of life-years saved after smoking cessation may have been underestimated.

The number of life-years saved per quitter tends to be smaller in studies based on disease-specific mortality (eg, PREVENT or HECOS model) than that based on comparisons of total mortality between smokers and quitter. For example, the PREVENT model compares deaths due to three smoking related diseases (lung cancer, CHD and COPD) between continued smokers and quitters. The average number of life-years saved per quitter by using the PREVENT model is 1.54 without discounting, and 0.99 using an annual discount rate of 1.5%.[22] Based on the total mortality of smokers and quitters from Doll et al.'s study of male doctors in England,[197, 199] the estimated number of life-years saved per lifetime quitter is:

	Undiscounted	Discounted (1.5%)

≤ 35	7.1	4.0
35-44	5.5	3.4
45-54	3.5	2.4
55-64	2.1	1.6

Doll et al.'s study showed bigger differences in life expectancy between cigarette smokers and quitters, based on a 40 year follow-up of male doctors (GPs) in England. An average of 2.8 life-years can be estimated by weighting the discounted number of life-years saved at different ages by the proportion of smokers who attempt to stop (personal communication: Dr John Stapleton).

For estimating the number of life-years saved per quitter for the whole population in modelling, however, the generalisability of Doll et al.'s results must be questioned. For example, quitters in Doll's study had smoked about 10% less cigarettes per day than continued smokers of the same age.[199] The cigarettes consumed by smokers in Doll's study were unfiltered, which may be more harmful than the filtered cigarettes.[185] In addition, it is impossible to exclude the impacts of other socioeconomic factors on differences in mortality between quitters and continued smokers in Doll's study.

An assessment of the results from the range of studies (see Appendix 9.10) and consideration of results from Doll's study suggests that a figure of 1.0 to 3.0 life-years saved per long-term quitter seems reasonable.

Quality adjusted life-years saved

A more important outcome is the number of quality-adjusted life-years (QALY) saved after quitting cigarette smoking. This, however, is more problematic to calculate than life years saved (LYS). According to limited data, the quality of life of quitters has been reported to improve after smoking cessation. If so, it has been argued that the cost-effectiveness of smoking cessation was underestimated in studies that failed to adjust for quality of life.[187]

Fiscella and Franks[187] have estimated quality-adjusted life-years saved after smoking cessation, using the Healthy People 2000 Years of Healthy Life (YHL) measure in the United States.[198] They calculated that the number of QALYs associated with a quitter on average was about 1.98 (range 0.69 - 2.38). In this study the quitters are lifetime quitters who did not smoke again (assuming that the lifetime probability of relapse is 35%). If the number of quitters at 12 months is used, the corresponding number of QALYS per quitter is 1.29 (range, 0.45, 1.55).

Using similar methods, Cromwell et al.[186] have estimated that on average the number of QALYS was 1.97 per long-term quitter (or 1.08 per quitter at 12 months).

It appears that the number of QALYs per quitter should be around one third greater than the number of life-years saved per quitter, but this requires further work and may well be sensitive to the discount rate (short term losses and longer term gains in QOL due to quitting.)

5.1.4 Estimating costs of smoking cessation interventions

The viewpoint for analysis

The viewpoint for analysis has been generally that of the payers in the existing economic evaluation of smoking cessation interventions (see Appendix 9.10). A few studies also provided results from the viewpoint of society or employers (who may be payers of healthcare insurance in the US). In the UK studies, the viewpoint for analysis is both NHS and/or Society,[22] the NHS [182] [183, 184] and the payers.[185]

Direct costs of smoking cessation interventions

In studies that have adopted the viewpoint of payers, the costs associated to smoking cessation interventions mainly include GP or nurse time, educational material, and NRT patch or gum. The estimated costs are often not discounted because the expenditure is short-term within one year. Future costs, particularly costs averted by health services, because treatment of disease is avoided, are not included in most studies. The justification for excluding future health care costs averted is that there is uncertainty as to whether the reduced costs to the health services are off-set by the increased costs of providing other health services as well as pensions and reduced tax revenue. In any case, the effects of discounting future costs to net present values would greatly reduce them, given the long time before they occur.

Empirical evidence indicates that smokers who failed to quit after a week of smoking cessation intervention are unlikely to abstain despite continued treatment.[200-202] Thus, a study has adopted an approach of abstinence-contingent treatment (ACT model).[185] In the ACT model, physicians continue giving pharmacological treatment only to those who abstain at each point of follow-up. The ACT model may reduce the cost without unfavourable impact on the effectiveness of the smoking cessation intervention.

Long-term medical expenditure

There are different opinions about the impact of smoking cessation on the long-term medical expenditure. One study suggests that smoking cessation may reduce the health care costs in the short term but would increase the health care costs eventually. [203] This conclusion, has been disputed as has been stated in several published letters.[204] [205] [206] [207] [208] It should be noted that discounting reduces the present value of the costs of long term medical expenditures so that they are unlikely to have much impact on estimates of cost-effectiveness.

The long-term economic outcomes of smoking have been estimated by using the Health and Economic Consequences of Smoking (HECOS) model.[184] It is reported that in the UK, the direct medical costs associated with smoking related morbidity are about £28.3 billion after 20 years (UK£, 1999; annual discount rate 6%). The impact of smoking cessation on long-term medical expenditure has not been considered in most of the studies because of lack of accurate data and great uncertainty. The principal objective of health care interventions, it has been argued, should be to produce health gains such as a healthier population with a longer life expectancy.[209]

5.1.5 Cost-effectiveness of smoking cessation interventions

The cost-effectiveness of smoking cessation interventions can be presented as cost per quitter, cost per life-year saved, or cost per QALY saved.

Cost per quitter

Cost per quitter is easiest to estimate, and is useful when comparing different smoking cessation interventions. A UK study has estimated that the average costs per quitter are £172 for brief advice, £218 for advice plus self-help materials, £267 for advice plus self-help materials plus NRT, and £252 for smoking cessation clinics (UK£, 1997).[22] In the study using the HECOS model, the average costs per quitter are £92 for advice only, £649 for pharmacological therapy, and £1148 for group therapy (UK£, 1999).

Higher costs per quitter are derived from monitoring the new smoking cessation services set up in Health Action Zones (HAZs) in England during the year April 1999 to March 2000. [210] The Department of Health reported that the cost per successful quitter (based on self report at the 4 week follow-up) was about £870. Twenty-six HAZs have been established in England by the government in areas of deprivation and poor health. The monitored smoking cessation services include specialist clinics and intermediate interventions. During the year 1999/2000, 14,598 smokers set a quit date through the smoking cessation services and 39.5% of them have successfully quit (based on self report at the 4 week follow-up). The

total expenditure from the special allocation is £5,026,000, including cost of staff (£2,070,000), training (£268,000), advertising/promotion of services (£836,000), accommodation (£200,000), computer equipment (£195,000), NRT supplied free to clients (£142,000), and other (£1,315,000). It should be noted that the cost of OTC NRT has not been included. The average cost per quit attempt (with a quit date) is £344 (i.e., £5,026,000/14,598), which is higher than that in many existing economic evaluations. This may be due to different definition of smoking cessation attempts and due to the infrastructure required to implement the programmes.

Cost per life-year saved

The costs per life-year saved after smoking cessation range from less than £200 to more than £4500, according to several UK studies (Appendix 9.10). Parrott et al. reported that the average cost (UK£, 1997) per life-year saved is £174 for brief advice, £221 for advice plus self material, £269 for advice plus self material plus NRT, and £255 for special smoking cessation clinics, from a viewpoint of the NHS.[22] In the published HECOS model, the average cost per life-year saved is £1212 (UK£, 1999).[184]

In a major US study,[186] the average cost (US$, 1996) per life-year saved is $1496 - $5423 by counselling without NRT, $1581 - $3248 by counselling plus NRT patch, or $2461 - $6135 by counselling plus NRT gum (from payers viewpoint).

Cost per QALY saved

Two US studies have estimated cost per quality-adjusted life-years saved as US$4546 to $10943[187] and US$1108 to $4542.[186]

Incremental cost-effectiveness of NRT and/or bupropion SR

Several studies have reported incremental cost of NRT per life year saved. Parrott et al. estimate that the incremental cost per life-year saved is £660 (the NHS perspective).[22] After adding NRT to advice, the incremental cost per extra life-year saved is estimated to be £4526 (UK£, 1992) for patch (UK£, 1992)[181] and £1527 for nasal spray (UK£, 1993)[181] in two studies by Akehurst and Piercy, or from £345 to £785 (UK£, 1998) in the study by Stapleton et al.[185]

The incremental cost per life year saved by adding NRT to counselling is $4140 - $8421 (US$, 1984) according to Oster et al., [188] $4546 - $10943 (US$, 1995) according to Fiscella et al.,[187] and $1822 - $3686 according to Wasley et al.[189]

5.1.6 Commentary

Dealing with uncertainty

Sensitivity analysis has been used in the most of the existing studies of economic evaluation of smoking cessation interventions. In the study by Fiscella and Franks,[187] Monte Carlo simulation was also used.

In a UK study by Stapleton et al., the incremental cost-effectiveness of GP advice plus NRT patch was shown to be sensitive to the quit rate, the cost of NRT patch, life-years saved by stopping smoking, and the relapse rate after 12 months of abstinence.[201] The results were shown to be sensitive to the discount rate used for life-years saved in the study by Fiscella & Franks[187] and by Cromwell et al.[186]

Overall, the results of sensitivity analyses from different studies suggest that even the pessimistic estimates of cost-effectiveness of smoking cessation interventions compare favourably with other healthcare interventions.

Intensity of smoking cessation interventions

Warner identified that less resource-intensive interventions (e.g., self-help materials) were more cost-effective than more resource-intensive interventions (e.g., GP advice plus NRT).[211] As the intensity of smoking cessation interventions increases, both cost and effectiveness increase, but cost increases more rapidly. For example in Parrott et al.[22] the estimated incremental cost per life-year saved is £174 by brief advice only. The incremental cost per life-year saved by adding self help material to GP advice is £362. On adding NRT to GP advice and self help material, the incremental ratio increases to £660.

This observation should not be used to reject the use of more resource-intensive interventions for at least two reasons. First, the assumption that all smokers have the same response to a particular intervention is unlikely to be true. Some smokers may only respond to more resource-intensive interventions, although it may be difficult to predict who will respond to a given intervention. Second, the incremental cost-effectiveness ratio of more resource-intensive interventions still compared favourably with many accepted healthcare interventions. The incremental cost per life-year saved is from $1,822 to $10,943 by smoking cessation interventions. According to Tengs et al., the median medical intervention costs $19,000 per life-year saved.[212]

Generalisability

There may be questions about whether the results of trials can be generalised to the population. A further issue is the possible changes in cost-effectiveness as programmes expand. At the early stage of a smoking cessation programme, there may be a large number of smokers who find it relatively easy to give up smoking. Over time, the proportion of smokers who fail to respond to interventions will increase. Consequently, the quit rate due to the same interventions may decline.[209] The infrastructure costs of programmes may also need to be taken into account.

In a study by Buck and Morgan,[213] smokers who found it hardest to give up were more likely to use NRT and multiple cessation aids. Self help material or brief GP advice may be the most cost-effective intervention for smokers who are highly motivated and/or can quit easily without any aid. NRT or bupropion SR may be the most cost-effective for smokers who are deeply addicted to nicotine. The population of smokers is clearly not homogeneous, but studies of cost-effectiveness have not attempted to separate smokers into different subgroups.

5.1.7 Remarks about existing economic evaluation studies

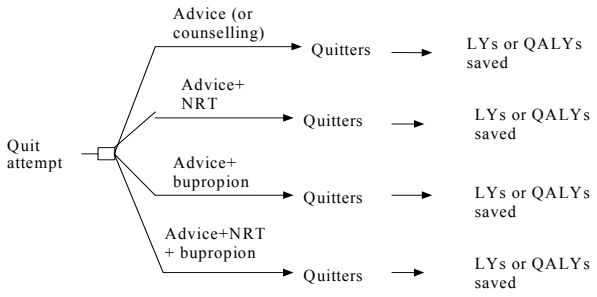
1. Irrespective of the methods used or assumptions involved, the results of existing economic evaluations consistently suggest that smoking cessation interventions are relatively cost-effective in terms of cost per life-year saved.
2. Adding NRT to the current practice is cost-effective, with a relatively low (under £1k) incremental cost per quitter. No published study has evaluated the relative cost-effectiveness of SR for smoking cessation.
3. Based on results from trials, we can estimate the additional number of quitters by adding NRT or bupropion SR to advice or counselling. It is then simple to estimate the incremental years of life saved according to ratio of LYs/quitter from existing studies. (This is the purpose of the modelling reported in section 5.2.)
4. There are many parameters in the health economic models about which there is a high degree of uncertainty. Such parameters include lifetime relapse rates, quit rates based on biochemical confirmation versus self-report, discount rates, and the long-term health benefit after smoking cessation. However, the overall conclusions about the cost-effectiveness of smoking cessation interventions remain favourable even when rigorous sensitivity analysis has been applied, ie, the worst case scenarios still provide estimates of cost-effectiveness better than many other medical interventions.

5.2 DECISION ANALYSIS MODELLING

This decision analysis modelling aims to estimate the cost-effectiveness of NRT and/or bupropion SR for smoking cessation, compared to and in addition to advice, from the NHS perspective. The impact of these interventions on cost and effectiveness for the NHS in England and Wales, has also been estimated.

The model compares four smoking cessation interventions: advice or counselling only (including GP advice and more intensive counselling by other health professionals), advice plus NRT, advice plus bupropion SR, and advice plus NRT and bupropion SR (Figure 4). The advice or counselling only option is considered as the reference (control) for estimating incremental cost-effectiveness of NRT and bupropion SR for smoking cessation. To simplify the modelling, it is assumed that there is no crossover between different strategies (this may not be true in the real world but the results will be intermediate to the options modelled).

Figure 4. Model structure for estimating cost-effectiveness of smoking cessation interventions



5.2.1 Estimating effectiveness

The effectiveness outcome used in the model is the number achieving continuous abstinence at 12 months. In addition, the number of life-years saved (LYS) or QALYs saved, based on (1) the number of quitters (from the model) and (2) a ratio of LYS and QALYS per quitter (from the review of existing studies in section 5.1) have been estimated. More detailed descriptions concerning the methods are given below.

Relative effect of NRT and bupropion SR

In published studies, odds ratios are often used to estimate the relative efficacy of NRT or bupropion SR for smoking cessation. Where possible, the estimates of odds ratios are based on the results of meta-analyses of RCTs.[24, 40, 214] In the Cochrane review that includes more than 90 RCTs of NRT, the overall odds ratio for abstinence with NRT versus control was 1.73 (95% CI: 1.62, 1.85).[24] By including only the 70 RCTs with data for 12 months or more continued abstinence, the odds ratio with NRT versus control is 1.67 (95% CI: 1.55, 1.80).

In the Cochrane review of antidepressants for smoking cessation, pooling of the results from four trials yields an overall odds ratio of 2.73 (95% CI: 1.90, 3.94) with bupropion SR versus placebo.[40] When unpublished data are included, the relative efficacy of bupropion SR is smaller: the overall odds ratio with bupropion SR versus placebo becomes 2.1 (95% CI: 1.62, 2.73) for continuous abstinence at 12 months.

Only one trial that has evaluated the combination of bupropion SR and NRT for smoking cessation.[39] The direct comparison of bupropion SR plus NRT versus placebo yields an odds ratio of 3.0 (95% CI: 1.8, 4.9). In the same trial, the quit rate in the bupropion SR plus NRT group is higher than that in the bupropion SR group, but the difference is not statistically significant. The odds ratio with bupropion SR plus NRT versus bupropion SR alone is 1.26 (95% CI: 0.85, 1.88). Using the adjusted indirect methods,[215, 216] it could be estimated that the adjusted odds ratio with bupropion SR plus NRT versus placebo is 2.65 (95% CI: 1.65, 4.25).

Different methods can be used to estimate the relative efficacy of bupropion SR or bupropion SR plus NRT. The relative efficacy of bupropion SR or bupropion SR plus NRT estimated directly from a single RCT[39] is greater than that estimated by the adjusted indirect methods after including additional evidence from meta-analysis. Until the great benefit of bupropion SR or bupropion SR plus NRT in that trial could be confirmed by further trials, it seems more appropriate to adopt the conservative estimates by using the adjusted indirect comparison. This is the approach followed in the modelling reported below.

Continuous quit rate at 12 months

First the quit rate by advice or counselling only, based on data from the published economic evaluations[22, 184] of smoking cessation interventions is estimated. Excluding spontaneous cessation (1% per year), it is assumed that the continuous quit rate at 12 months is 3% by advice only and 9% by counselling only. Then the quit rate of NRT and bupropion SR can be

estimated by using the odds ratio and the quit rate in the control (advice or counselling only) group:

$$p1 = OR \times p2 / (1 - p2 + OR \times p2),$$

where *p*1 is the quit rate of NRT, or bupropion SR, or NRT+bupropion SR; *p*2 is the quit rate in the advice or counselling only group and *OR* is the odds ratio.

In this model, we examined two scenarios: brief advice with a control quit rate of 4%, and counselling with a control quit rate of 10%. Given a certain odds ratio, the absolute difference in quit rate of NRT or bupropion SR depends on the quit rate in the control (advice or counselling only) group (Table 17). For example, an odds ratio of 1.67 for NRT corresponds to a quit rate of 6.5% in the NRT group when the quit rate in the control (advice) group is 4.0%. The same odds ratio (1.67) corresponds to a quit rate of 15.7% in the NRT group when the quit rate in the control (counselling) group is 10.0%. The difference in the quit rate is 2.5% (i.e., 6.5%-4.0%) between the NRT+advice and the advice only group, and 5.7% (i.e., 15.7%-10.0%) between the NRT+couselling and the counselling only group.

The lifetime relapse rate is assumed to be 40% (range: 30-50%).

Life-years saved and quality-adjusted life-years saved (QALYS)

The number of quitters is transformed to the life-years saved using the ratio of life-years saved per long-term quitter (defined as those who never smoke again). According to a review of existing economic evaluations (see section 5.1.3), we assume that on average 2 life-years are saved per quitter, and the range of ratio of life-years saved per quitter is from 1.0 to 3.0. For simplification, the difference between age and gender groups is not considered.

Based on a ratio of 1.35 (QALYS/LYS) from Fiscella and Franks study, the number of QALYS per lifetime quitter is assumed to be on average 2.7 (range, from 1.35 to 4.05).[22]

5.2.2 Estimating cost of interventions

The estimates of cost of interventions are subject to some uncertainty. The average costs of different strategies are estimated by assuming that not all motivated-to-stop smokers will receive the full courses of treatment. Since only short-term cost is included in the model, costs are not discounted. The detailed assumptions are presented in Table 18, and further explanation follows below.

<u>Brief advice from a GP</u>

The cost of GP advice can be marginal or average. In the marginal scenario, a GP may offer smoking cessation advice as part of a consultation primarily concerned with another health matter. Best estimates put this at three minutes to deal with smoking cessation and a further three minutes if prescription is involved. Given that this consultation is taking place anyway, marginal costs apply, estimated by Netten et al. at £0.49 per minute.[217] Thus, for brief advice alone the costs would be £1.47 without prescription, and £2.94 if prescription is required.

Consultations may also be generated principally to discuss smoking cessation, which may become more common if it is widely known that doctors will issue prescriptions. In this case, full costs apply, which according to Netten et al., would be £13.80 (excluding the cost of any prescription).

It is unlikely that most people prescribed NRT will return for specific sessions to discuss side-effects. (They may enrol in smoking cessation counselling, though this is covered elsewhere). However, if consultations do occur, these will attract the full costs of £13.80. It is more likely that people taking bupropion SR will return for consultations at the same cost.

Drug costs

Bupropion SR is recommended for 7-9 weeks. Given it comes in two 4-week packs, we anticipate that it will be prescribed in two 4-week packs. However, some patients will not return for the second 4-week pack, because they have returned to smoking and abandoned this attempt at cessation. Judging from Jorenby et al.[39] around half of patients in counselling might have ceased to attend and hence not collect the second 4-week script. This is likely to be somewhat higher in the brief advice only patients.

NRT comes in a variety of formulations each with somewhat different lengths of therapy, which will affect costs. An average 4-week cost is £37, and in the cheapest scenario, all participants use it for 4 weeks, and one third return for one further 4-week course. In the most expensive scenario, all participants use it for four weeks, two thirds return for a further 4-week course, and half for a further 4-week course.

Counselling

Counselling can be provided within the NHS by intermediate-level or specialist-level services. Intermediate-level services are provided by practice nurses with some specialist training. They tend to offer up to six 10-20 minute sessions. Specialist services tend to be provided in groups with between five and 20 patients per group. Group leaders have variable training, but tend to be paid about what practice nurses are paid.

5.2.3 Main results of cost-effectiveness modelling

Cost per quitter

Table 19 presents the results of baseline estimates according to average values in various assumptions. Using brief advice as the standard intervention without pharmacological treatment, the average cost per lifetime quitter is £196 for advice only, £2288 for advice plus NRT, £1799 for advice plus bupropion SR, and £2683 for advice plus NRT and bupropion SR. The incremental cost per lifetime quitter is £4798 for advice plus NRT, £2986 for advice plus bupropion SR, and £3939 for advice plus NRT and bupropion SR.

When more intensive counselling is involved, the average cost per lifetime quitter is £653 for counselling only, £1173 for counselling plus NRT, £964 for counselling plus bupropion SR, and £1314 for counselling plus NRT and bupropion SR. The corresponding incremental costs per lifetime quitter is £2001 for counselling plus NRT, £1278 for counselling plus bupropion SR, and £1781 for counselling plus NRT and bupropion SR.

Table 20 presents the results of sensitivity analyses, using the most unfavourable estimates of effect and the most expensive scenario for cost. The most pessimistic estimates of incremental costs per lifetime quitter are £8413 for NRT, £7347 for bupropion SR, and £13,612 for NRT plus bupropion SR.

Cost per life-year saved and per QALYS

Based on the assumption that the number of life-years saved per lifetime quitter is 2.0 (range 1.0 , 3.0), and the number of QALYS per quitter is 2.7 (range 1.35, 4.05), Table 21 and Table 22 present costs per life-year saved and per QALY saved respectively. According to the baseline estimates, the incremental cost per life-year saved is about £1,000-2,399 for NRT, £639-1,492 for bupropion SR, and £890-1,969 for NRT plus bupropion SR.

Using the low estimates of effect and high estimates of cost, the most pessimistic result of cost per life-year saved is £8,413 for NRT, £7,347 for bupropion SR, and £13,612 for NRT plus bupropion SR.

According to the baseline estimates, the incremental cost per QALYS are about £741-1,777 for NRT, £473-1106 for bupropion SR, and £660-1,459 for NRT plus bupropion SR. The most pessimistic estimates of cost per QALYS are about £6,231 for NRT, £5,442 for bupropion SR, and £10,083 for NRT plus bupropion SR.

5.2.4 Impact on cost and effectiveness

The impact of NRT and bupropion SR on cost and effectiveness for NHS, in England & Wales, was estimated using results of the modelling and population data (Population Trends 98, Office of National Statistics).

The total number of adults aged 16 and over in England and Wales in 1998 was 41,746,000 and the prevalence of smoking was 27%. Thus the total number of smokers can be estimated as 11,271,420. Suppose 30% of smokers would use NHS smoking cessation services, the total number of quit attempts would be 3.4 million.

Table 23 presents the impact of smoking cessation interventions assuming only one strategy is available. The incremental estimate is perhaps most useful and also relatively accurate. Supposing only one strategy is available, the additional cost to the NHS in England and Wales is about £240 million for use of NRT or for bupropion SR, and about £470 million for NRT plus bupropion SR. The number of quitters increases along with the increase in cost.

It is more realistic to assume that smokers who attempt to quit may use different interventions. Tentatively, we assume that the proportion of users is 35% for advice or counselling only, 50% for advice+NRT, 10% for advice+bupropion SR, and 5% for advice+NRT+bupropion SR (Table 24). Then the total cost to the NHS is £202 million, the total number of attempts is about 3.4 million and the total number of lifetime quitter is about 135,000. Thus, the average cost per motivated-to-stop smoker and per lifetime quitter is about £59.6 and £1,500 respectively.

If the percentage of smokers who use NHS smoking cessation services is 10% and suppose only one strategy is available, the incremental cost to the NHS would be about £80 million for the use of NRT or bupropion SR and about £160 million for the use of NRT plus bupropion SR. If these users are distributed across different interventions, the total cost to the NHS would be £67 million, yielding 45,000 lifetime quitters and 90,000 life-years saved.

The cost per attempt and per quitter at 4 week is £344 and £870 respectively from the Health Action Zones (see section 5.1.5).[210] The high costs may be mainly due to the infrastructure required to implement the programmes, which do not appear to have been fully costed in the model. In a sensitivity analysis, assuming 20% of motivated-to-stop smokers use smoking cessation clinics with an average cost of £344 per attempt, it will cost a total of £78-£233 million. If the total cost for other 80% of GP advice users remains the same (£48.5-£145.5

million), the total cost of smoking cessation interventions to the NHS will be 126.5 -£378.1 million.

5.2.5 Summary of cost-effectiveness modelling

1. The results of this decision analysis modelling are similar to that of previous studies. The smoking cessation interventions using NRT and/or bupropion SR are cost-effective as compared with many accepted healthcare intervention. According to our estimates, the incremental cost per life-years saved is about £1,000-2,399 for NRT, £639-1,492 for bupropion SR, and £890-1,969 for NRT plus bupropion SR.
2. The estimated cost of the smoking cessation programme to the NHS in England and Wales would be about £67-202 million per year. Consequently, about 45,000-135,000 smokers will quit, and about 90,000-270,000 life-years may be saved. The average cost per life-year saved is about £750 (range £500 to £1,500).
3. According to the available evidence, the incremental cost-effectiveness of bupropion SR is generally better than that of NRT. However, this should be interpreted cautiously because of very limited data on the relative efficacy of bupropion SR and its possible side-effects.

Table 17. Estimating 12 month quit rate for NRT or bupropion SR based on odds ratio (point estimates and 95% CIs) and quit rate in the control group

	Point	Low CI	High CI	Point	Low CI	High CI
NRT versus control						
Control quit rate	0.0400	0.0400	0.0400	0.1000	0.1000	0.1000
Odds ratio	1.6700	1.5500	1.8000	1.6700	1.5500	1.8000
Treated quit rate	0.0651	0.0607	0.0698	0.1565	0.1469	0.1667
Rate difference	0.0251	0.0207	0.0298	0.0565	0.0469	0.0667
Bupropion SR versus control						
Control quit rate	0.0400	0.0400	0.0400	0.1000	0.1000	0.1000
Odds ratio	2.1000	1.6200	2.7300	2.1000	1.6200	2.7300
Treated quit rate	0.0805	0.0632	0.1021	0.1892	0.1525	0.2327
Rate difference	0.0405	0.0232	0.0621	0.0892	0.0525	0.1327
NRT plus Bupropion SR versus control						
Control quit rate	0.0400	0.0400	0.0400	0.1000	0.1000	0.1000
Odds ratio	2.6500	1.6500	4.2500	2.6500	1.6500	4.2500
Treated quit rate	0.0994	0.0643	0.1504	0.2275	0.1549	0.3208
Rate difference	0.0594	0.0243	0.1104	0.1275	0.0549	0.2208

Table 18. Estimated costs of smoking cessation interventions

	Cheapest scenario	Average scenario	Most expensive scenario
Brief advice			
Brief advice alone	All consultations opportunistic. No reconsultation for smoking cessation advice. Cost £1.47	One sixth of consultations specifically for smoking cessation brief advice. Cost=£1.47*5/6+£13.80*1/6=£3.53	One third of consultations specifically for smoking cessation brief advice. Cost=£1.47*2/3+£13.80*1/3=£5.58
Brief advice with NRT prescription	All consultations opportunistic. 10% of patients reconsult for discussion of medication/ side-effects. Cost= £2.94+0.1*£13.80. Cost £4.32	One sixth of consultations specifically for smoking cessation brief advice and 30% of patients reconsult once. Cost=£1.47*5/6+£13.80*1/6+£13.80*0.3 =£7.67	One third of consultations specifically for smoking cessation brief advice and half of patients reconsult once. Cost=£1.47*2/3+£13.80*1/3+£13.80*0.5 =£12.48
Brief advice with bupropion SR prescription	All consultations opportunistic. 10% of patients reconsult for discussion of medication/ side-effects. Cost £2.94+0.1*£13.80. Cost £4.32	One sixth of consultations specifically for smoking cessation brief advice and 60% of patients reconsult once. Cost=£1.47*5/6+£13.80*1/6+£13.80*0.6 =£11.80	One third of consultations specifically for smoking cessation brief advice and all patients reconsult once. Cost=£1.47*2/3+£13.80*1/3+£13.80 =£19.38
Drugs			
Bupropion SR	All patients cash in prescription 1, but one third return for second 4-week prescription. Cost=£42.85+£42.85*1/3=£57.13	All patients cash in prescription 1, but half return for second 4-week prescription. Cost=£42.85+£42.85*1/2=£64.28	All patients cash in prescription 1, but two thirds return for second 4-week prescription. Cost=£42.85+£42.85*2/3=£71.42
NRT	All patients cash in prescription 1, but one third return for second 4-week prescription. Cost=£37+£37*1/3=£49.33	All patients cash in prescription 1, but half return for second 4-week prescription, and a third for third 4 week prescription. Cost=£37+£37*1/2+£37*1/3=£67.83	All patients cash in prescription 1, but two thirds return for second 4-week prescription, and half for third 4 week prescription. Cost=£37+£37*2/3+£37*1/2=£80.17
Counselling			
Individual 'intermediate' counselling	All patients use 4 weeks of counselling, one third return for weeks 5 and 6. Sessions with nurse cost £0.47 per minute and last 10 minutes each. Cost =(£0.47*10*4)+(£0.47*10*2*1/3) =£21.93	All patients use 4 weeks of counselling, half return for weeks 5 and 6. Sessions with nurse cost £0.47 per minute and last 15 minutes each. Cost =(£0.47*15*4)+(£0.47*15*2*1/2) =£35.25	All patients use 4 weeks of counselling, two third return for weeks 5 and 6. Sessions with nurse cost £0.47 per minute and last 20 minutes each. Cost =(£0.47*20*4)+(£0.47*20*2*2/3) =£50.13
Specialist group counselling	Session uses 1 hour of nurse time and 6 are run. 20 patients per session. Cost=£0.47*60*6/20 =£8.46	Session uses 1.5 hours of nurse time and 6 are run. 10 patients per session. Cost=£0.47*60*1.5*6/10 =£25.38	Session uses 2 hours of nurse time and 6 are run. 5 patients per session. Cost=£0.47*60*2*6/5 =£67.68

Table 19. Baseline estimates of cost-effectiveness of smoking cessation interventions

Strategy	Cost per attempt (£)	12 month Quit rate	Lifetime quit rate	Average costs per lifetime quitter	ICER1	ICER2	ICER3
Using brief advice as standard intervention							
Brief Advice only	3.53	0.0300	0.018	196	-	-	-
BA + NRT	75.5	0.0550	0.033	2288	4798	-	-
BA+bupropion SR	76.08	0.0705	0.0423	1799	2986	62	-
BA+NRT+bupropion SR	143.91	0.0894	0.0536	2683	3939	3314	5981
Using counselling as standard intervention							
Counselling	35.25	0.0900	0.0540	653	-	-	-
Couns+ NRT	103.08	0.1465	0.0879	1173	2001	-	-
Couns+bupropion SR	103.66	0.1792	0.1075	964	1278	30	-
Couns+NRT+bupropion SR	171.49	0.2175	0.1305	1314	1781	1606	2952

Note:
1. ICER is the incremental cost-effectiveness ratio (cost £ per lifetime quitter).
2. ICER1, using the brief advice only or counselling only as the reference.
3. ICER2, using the brief advice plus NRT or counselling plus NRT as the reference.
4. ICER3, using the brief advice plus bupropion SR or counselling plus bupropion SR as the reference.

Table 20. Average and incremental costs per lifetime quitters for different smoking cessation interventions: sensitivity analyses.

Assumptions		Advice only	Advice + NRT	Advice + bupropion SR	Advice+NRT +bupropion SR
Low effect model – 1	ARCE	235	2978	2860	5301
Advice quit rate = 0.03	IRCE1	-	6954	6254	11,554
Average estimates of costs	IRCE2		-	464	38,006
Lower estimates of effect	IRCE3			-	123,327
Low effect model – 2	ARCE	783	1,506	1,455	2,367
Advice quit rate = 0.09	IRCE1	-	2,893	2,606	4,963
Average estimates of costs	IRCE2		-	207	17,103
Lower estimates of effect	IRCE3			-	56,525
High costs model – 1	ARCE	310	2,808	2,147	3,187
Advice quit rate = 0.03	IRCE1	-	5,805	3,507	4,641
High estimates of costs	IRCE2		-	dominate	3,795
Average estimates of effect	IRCE3			-	7,070
High costs model – 2	ARCE	928	1,482	1,195	1,600
Advice quit rate = 0.09	IRCE1	-	2,365	1,463	2,072
High estimates of costs	IRCE2		-	dominate	1,839
Average estimates of effect	IRCE3			-	3,489
Low effect and high costs model - 1	ARCE	372	3,655	3,414	6,297
Advice quit rate = 0.03	IRCE1	-	8,413	7,347	13,612
High estimates of costs	IRCE2		-	dominate	43,511
Lower estimates of effect	IRCE3			-	145,764
Low effect and high costs model - 2	ARCE	1,114	1,904	1,803	2,880
Advice quit rate = 0.09	IRCE1	-	3,419	2,984	5,774
High estimates of costs	IRCE2		-	dominate	19,580
Lower estimates of effect	IRCE3			-	66,808

Note: dominate indicates that bupropion SR dominates NRT in these cases.

Table 21. Costs per life-year saved: baseline estimates and according to different ratio of LYS per quitter

LYS/quitter	2.0	2.0	1.0	1.0	3.0	3.0
	Average	Incremental	Average	Incremental	Average	Incremental
Brief advice as standard reference						
Advice only	98	-	196	-	65	-
Advice+NRT	1144	2399	2288	4798	763	1599
Advice+bupropion SR	899	1493	1799	2986	600	995
Advice+NRT+bupropion SR	1341	1969	2683	3939	894	1313
Counselling as standard reference						
Counselling alone	326	-	653	-	218	-
Counsel+NRT	586	1000	1173	2001	391	667
Counsel+bupropion SR	482	639	964	1278	321	426
Counsel+NRT+bupropion SR	657	890	1314	1780	438	594

Table 22. Costs per quality-adjusted life-year saved: baseline estimates and according to different ratio of QALYS per quitter

QALYS per quitter	2.7	2.7	1.35	1.35	4.05	4.05
	Average	Incremental	Average	Incremental	Average	Incremental
Brief advice as standard reference						
Advice only	73	-	145	-	48	-
Advice+NRT	847	1777	1695	3554	565	1185
Advice+bupropion SR	666	1106	1332	2212	444	737
Advice+NRT+bupropion SR	994	1459	1987	2918	662	973
Counselling as standard reference						
Counselling alone	242	-	484	-	161	-
Counsel+NRT	434	741	869	1482	290	494
Counsel+bupropion SR	357	473	714	947	238	316
Counsel+NRT+bupropion SR	487	660	973	1319	324	440

Table 23. Estimated impact of smoking cessation interventions, England and Wales Assuming only one strategy is available

	Total attempts	Total cost (million, £)	Incre costs (million, £)	Total lifetime quitters (1,000)	Incre quitters (1,000)
Brief advice only	3381426	11.94		61	
BA+NRT	3381426	255.30	243.36	112	51
BA+bupropion SR	3381426	257.26	245.32	143	82
BA+NRT+bupropion SR	3381426	486.62	474.68	181	121
Counselling only	3381426	119.20		183	
Couns+NRT	3381426	348.56	229.36	297	115
Couns+bupropion SR	3381426	350.52	231.32	364	181
Couns+NRT+bupropion SR	3381426	579.88	460.69	441	259

Assumptions: 1. 30% of smokers will use NHS smoking cessation interventions. 2. According to baseline estimates (in Table 24)

Table 24. Estimated impact of smoking cessation interventions, England and Wales Assuming motivated-to-stop smokers distributed between different strategies

	Percent attempt to stop	Distribution between advice or counselling	Distribution between SC interventions	Total users	Costs (million, £)	Quitters (1,000)
Brief advice only	0.3	0.8	0.35	946799	3.34	28.40
BA+NRT	0.3	0.8	0.50	1352570	102.12	74.39
BA+bupropion SR	0.3	0.8	0.10	270514	20.58	19.07
BA+NRT+bupropion SR	0.3	0.8	0.05	135257	19.46	12.09
Counselling only	0.3	0.2	0.35	236700	8.34	21.30
Couns+NRT	0.3	0.2	0.50	338143	34.86	38.89
Couns+bupropion SR	0.3	0.2	0.10	67629	7.01	8.83
Couns+NRT+bupropion SR	0.3	0.2	0.05	33814	5.80	5.05
Total				3381426	201.52	208.03

Note: The estimates are based on the results using baseline assumptions (in Table 19)

6 DISCUSSION

6.1 MAIN EFFECTIVENESS RESULTS

6.1.1 Effectiveness of NRT

The effectiveness of NRT has been investigated in a large number of, mostly placebo controlled studies. These data demonstrate the effectiveness of NRT compared with placebo or no treatment in smoking cessation. Although the majority of studies have been performed with NRT gum or NRT patches, there are sufficient data with other forms of NRT to indicate that no difference in levels of effectiveness are to be expected. Pooling across all studies of NRT and including all types of NRT there is evidence of statistical heterogeneity. It appears likely that at least some of this heterogenaity arises due to clinical diversity within the gum and patch studies. Scope for investigating this within the present systematic review is limited due to its being a review of reviews, and therefore dependent upon the inclusion criteria of the primary systematic reviews. Overall the pooled estimates of effectiveness for each type of NRT demonstrate a benefit of NRT. The inclusion of the diverse gum and patch studies is likely to have underestimated the true level of effectiveness of NRT overall.

The evidence to support any differences in the level of effectiveness in sub-groups is weak. Such differences are not to be expected; there being no real basis to suspect NRT might have different effects in different smoking populations. The present review was unable to investigate any correlation between the number of previous attempts made to give up smoking and abstinence rates with NRT. Such an analysis would in any case be simplistic and could be confounded by many uncontrollable factors, e.g. methods used in previous quit attempts; and changes in participant's circumstances.

No analysis of self-referred patients versus physician referred has been possible in this review. Some evidence can be gleaned from an indirect comparison of the abstinence rates in primary care and community volunteers: the latter group being mainly recruited through media advertisements. This indirect comparison does not indicate any difference in success rates between these forms of NRT. Compounding the weak nature of this evidence are other factors such as different levels of motivation between the two populations.

A direct comparison of motivated with non-motivated smokers has also not been possible. It might be expected that a population of individuals that enrol in clinical trials, with the extra interest that such a process involves, would be more motivated and they would have more support to maintain their motivation, than in the non-trial setting.

Evidence relating to the different factors that can affect the level of effectiveness to be gained with NRT suggests that the use of higher doses of NRT may be beneficial in high-dependency smokers, but not in the general population. Evidence to support the use of combinations of NRT types is weak and probably overlaps with that for high doses of a single type. The use of high-doses of NRT versus combination of different NRT types is probably best determined by adverse effects rather than effectiveness levels. This is also true for a comparison between the 16-hour or 24-hour NRT patches.

No real conclusions can be drawn regarding the relative effectiveness of different durations of NRT therapy, nor the relative effectiveness of fixed schedule versus *ad libitum* dosing, or the gradual weaning of participants off NRT therapy versus abrupt withdrawal. There is some indication that high levels of motivational support can improve the absolute abstinence rates whilst maintaining the differential between NRT and placebo is maintained. Thus, NRT plus high level motivational support should give the highest levels of abstinence. Unfortunately, this issue could not be investigated properly within the confines of this review

There is no evidence to suggest that clinical setting is a critical factor per se in successful smoking abstinence.

Other than bupropion SR, no other active intervention has been found to be comparable with NRT.

6.1.2 Effectiveness of bupropion SR

The number of studies of bupropion SR in smoking cessation is relatively small, however, they are mainly of high quality and the level of evidence is good. There is clear evidence that bupropion SR is more effective than placebo, with no indication that bupropion SR is less effective in smokers with chronic obstructive pulmonary disease (COPD). The relative efficacy of bupropion SR and placebo are maintained when used to aid smoking cessation in people who have previously failed to achieve smoking abstinence whilst using bupropion SR. There is no information to compare physician referred or self referred

smokers, nor motivated with non-motivated smokers: all participants in trials of bupropion SR appear to have been selected specifically as 'motivated to quit'. Based on the lack of safety data, bupropion SR should not be used in pregnant women

There is evidence from a single study to suggest that bupropion SR is not effective for long-term use for the prevention of relapse in people who have succeeded in stopping smoking. This evidence combined with the increased risk of seizure with bupropion SR with time, indicates strongly that the long-term use of bupropion SR for prevention of relapse is not warranted.

6.1.3 Effectiveness of NRT versus bupropion SR

Evidence to support the superiority of bupropion SR over NRT for smoking cessation is weak, with only a single published study indicating that the NRT patch is less effective than bupropion SR. There is a hint from the available data that the combination of these two classes of smoking cessation aids may increase effectiveness. Further double-blind RCTs are required.

6.2 MAIN ADVERSE EFFECTS AND SAFETY RESULTS

6.2.1 Adverse effects and safety of NRT

Any discussion of the adverse effects and safety of NRT in smoking cessation has to be within the context of continuing smokers' self-administration of the active pharmacological agent of NRT, i.e. nicotine.

Overall, the incidence of adverse events with NRT is very low. The main concern regards potential adverse cardiovascular effects i.e. the same harmful effects that are the driving force behind needing to 'treat' smoking as a chronic illness. There is strong evidence that the effects of nicotine acquired through NRT are no different from those of smoking-derived nicotine. Evidence suggests that the main problem with NRT is that its use can delay the reversal of the adverse effects of smoking normally associated with smoking cessation. There is evidence to suggest that the abuse potential of NRT is low. However, it is possible that more could be done to promote cessation of NRT use once smoking abstinence is **firmly** established.

There is only very limited overlap of adverse symptoms associated with the different types of NRT. Thus, the qualitative differences of the adverse effects associated with the different types of NRT will determine their effectiveness in different individuals.

6.2.2 Adverse effects and safety of bupropion SR

The adverse event profile and safety of bupropion SR has to be considered carefully, given that it is to be used in mainly 'healthy' smokers rather than patients with a debilitating illness. Bupropion SR is taken for a short period of around nine weeks (or multiples there of). These factors have to be balanced when considering its safety.

To obtain as complete an overview of the adverse effects and safety of bupropion SR as possible, data pertaining to the original IR formulation of the drug as well as the SR formulation licensed for smoking cessation were considered. The primary difference to be expected between two such formulations would be that the peak plasma concentrations achieved with the SR formulation would be considerably lower than those achieved with the IR formulation. Theoretically this should result in a reduction of dose-related adverse events. In addition, studies of bupropion IR and SR used as an antidepressant were also included in this review. This was considered acceptable since the adverse events experienced are likely to be similar in people trying to stop smoking and in people with depression; with no physiological reason why they should be different. All participants included in the trials for either indication are likely to be reasonably physically well: otherwise they would be excluded prior to enrolment.

None of the common adverse events of bupropion (rash and pruritus, irritability, insomnia; dry mouth; headache; tremor; urticaria, rash; urticaria; insomnia; headache; dry mouth; and tremor) reported in this review are newly identified. The adverse events resulting in withdrawal from treatment with bupropion SR are the same as those with the IR formulation (skin disorders (mainly rash), insomnia, tremor, headache, dry mouth and anxiety) with the exception of motor disturbances, psychological problems, drowsiness, weight loss, headache/nasal congestion, thinking difficulties, dizziness, and tachycardia/palpitations. Such differences might be due to differences in dose, duration of treatment and differences in response between depressed and non-depressed patients. Significantly, the side effect profile of SR does appear to be better than that of IR.

As was already recognised, this review has identified seizure as the most significant and important potential adverse effect of bupropion. The crude incidence of seizure is lower with the SR than with the IR formulation, however the evidence demonstrates that even in populations screened to exclude those at risk, seizures can occur. Post-marketing safety monitoring demonstrates a significant level of seizures occurring in individuals treated with bupropion SR. This is possibly related to inappropriate prescribing or not adequately strict screening for seizure potential. Significantly, no RCT of bupropion SR in smoking cessation has reported any seizures. This may be related to stricter screening in the clinical trial setting than occurs in clinical practice, or may reflect the reduced risk with shorter-term use (the evidence points to an increased risk with longer use).

6.3 ECONOMIC EVALUATION

Results of studies of economic evaluations have consistently shown that smoking cessation interventions are cost-effective in saving lives, compared with many other accepted therapeutic and preventive health care interventions.

A new model was developed both because previous studies did not explicitly compare bupropion SR with the range of alternative interventions and also because it seemed valuable to separate the short and long term effectiveness, given the uncertainties involved with the latter. Our model has explicitly stated the assumptions about the number of life-years saved per quitter, based on a synthesis of results from many existing economic evaluations of smoking cessations.

The results of this decision analysis modelling are broadly similar to that of previous studies. The smoking cessation interventions using NRT and/or bupropion SR are cost-effective as compared with many accepted healthcare interventions. According to our estimates, the incremental cost per life-years saved is about £1,000-2,300 for NRT, £640-1,500 for bupropion SR, and £900-2,000 for NRT plus bupropion SR. Our analysis extends the previous literature by comparing bupropion SR with NRT, showing that the former has a lower incremental cost-effectiveness ratio than the latter.

A number of weaknesses of the model can be identified. The model considers only patients who remain on one type of treatment, whereas patients may move from treatment to treatment. However, as noted above, these patients will have a cost effectiveness ratio

intermediate to those shown in the model. Other assumptions have to do with the natural quit rate and the generalisability of the trial results on effectiveness.

The cost per LY and QALY estimates are based on many assumptions covering quitters or smokers lifetimes, and hence subject to greater uncertainty. In particular, the effectiveness of smoking cessation interventions may have been over-estimated because the model does not consider the impact of possible changes in natural quit rate after smoking cessation interventions. If the quitters following interventions tend to be those who would stop spontaneously in future, the effect of smoking cessation interventions will be considerably reduced.

The cost of smoking cessation interventions may become lower if an abstinence-contingent-treatment (ACT) approach has been used. On the other hand, the cost of smoking cessation interventions appears to be understated in the model, considering the data on higher cost per attempted quitter from the Health Action Zones.

While the results of the modelling should be interpreted cautiously, because of the uncertainties discussed above, the range of smoking cessation interventions nonetheless appear to be cost-effective relative to widely accepted health care interventions, even if the pessimistic estimates are considered.

The estimated cost of bupropion SR for smoking cessation is similar to that of NRT. Based on limited data from only two trials, the effect of bupropion SR is greater than NRT. Although we have used conservative estimates for the effectiveness of bupropion SR in our model, the cost-effectiveness ratio of bupropion SR is still on average more favourable than that of NRT. However, this result should be handled with care. First, the data available on bupropion SR are far more limited than data available on NRT. The use of conservative estimates of bupropion SR's effectiveness cannot completely exclude the possibility that relative efficacy of bupropion SR for smoking cessation has been overestimated. More importantly, use of bupropion SR needs more health professionals' supervision because of rare but potentially serious side effects. The possible costs and health consequences due to bupropion SR's side effects have not been considered in the modelling.

6.4 ASSUMPTIONS, LIMITATIONS AND UNCERTAINTIES

Due to time constraints and the wide scope of this review the clinical effectiveness section was based on a review of existing systematic reviews of effectiveness rather than all primary studies. This limited the exploration of the data, mainly to those conducted in the primary systematic reviews. The analyses and investigations into the data omitted because of this are discussed in section 6.3 above. In addition, the balance of decreased individual effectiveness against population coverage has not been addressed.

6.5 NEED FOR FURTHER RESEARCH

The data on effectiveness and adverse effects of NRT and bupropion SR seem comprehensive and only studies that investigate the effectiveness of NRT compared with bupropion SR appear necessary. Ideally these would include a level of motivational support that was the maximal that could realistically be provided within the provision for smoking cessation.

Assuming all participants included in the studies were motivated to quit, the questions to ask now may be

- How do we encourage smokers to become motivated to quit?
- How do we effectively maintain them in a motivated to quit state until smoking cessation has been achieved?

7 CONCLUSIONS

- Both NRT and bupropion SR are effective interventions to assist smoking cessation.
- The relative effectiveness of bupropion SR and NRT still needs further research.
- Information on how to maximise effectiveness in practice is still lacking, but probably involves motivational support.
- The most significant differences between NRT and bupropion SR relate to the adverse events and safety profiles of these interventions.
- Overall, the safety profile of NRT is more favourable, particularly given the small but real risk of seizure with bupropion SR.
- Irrespective of methods used or assumptions involved, the results of existing economic evaluations and the model developed in this review consistently suggest that smoking

cessation interventions, including use of NRT and/or bupropion SR, are relatively cost-effective in terms of cost per life-year saved. The worst case scenarios still provide estimates of cost-effectiveness better than many other medical interventions.

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9 APPENDICES

9.1 LIST OF MEMBERS OF EXPERT PANEL

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9.2 SEARCH STRATEGY

9.2.1 LITERATURE SEARCHING CHAPTER

A wide range of databases and other information resources were searched to locate details of both published and unpublished studies, and other information on the effectiveness, cost-effectiveness and safety of bupropion SR (Zyban®) and nicotine replacement therapy (NRT) for smoking cessation. A total of 25 electronic databases were searched, and searches of the World Wide Web were also undertaken. Full details are provided in Appendix 9.2.

The search strategies were devised by the Information Service Team at the NHS Centre for Reviews and Dissemination, University of York, and were checked by the review team.

Structure of the literature searches

To locate references on the effectiveness of bupropion SR and NRT in smoking cessation, literature searches initially focussed on identifying all relevant **systematic reviews** in the area.

A search strategy was then devised to identify any newly-published **randomised controlled trials** in order to update the references retrieved by previous systematic review searches.

For information relating to the **adverse effects and safety** of bupropion, literature searches were designed to retrieve studies of any design and systematic reviews wherever possible.

Searches on the **cost-effectiveness** of bupropion and NRT were conducted separately. No limits by study design were applied.

All initial searches were carried out between December and February 2001, and subsequently updated in April/May 2001. Resources were searched from their date of inception to the most recent date available at that time. There was no restriction of study by country of origin, language or date of publication, although non-English language papers were not selected for inclusion in the review.

The bibliographies of retrieved references were scanned for further relevant publications.

References were managed using the EndNote4 software.

Search strategy

The core search strategy used for this review was as follows:

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
smok* or tobacco or nicotin*
#3 and #4
nicotine replacement therap*

nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7 or #8
#5 or #9

This strategy was designed for searching the MEDLINE electronic database (on SilverPlatter), and was adapted as appropriate for all other databases searched, taking into account differences in indexing terms and search syntax for each database. 'Buproprion' was used as a search term, as this appeared to be a commonly occurring spelling mistake.

The search strategy was subsequently modified to limit results by study type, to adverse effects/safety studies only, or cost-effectiveness studies only.

9.2.2 DATABASES

The databases searched for each aspect of the review are presented in tabular form below.

Database - Host	Systematic reviews	RCTs	Adverse effects	Cost-effectiveness
AMED - SilverPlatter			✔	
Biosis - Edina		✔	✔	
CancerLit - SilverPlatter		✔		
CINAHL - SilverPlatter	✔	✔	✔	
Cochrane Controlled Trials Register - Cochrane Library CD-ROM		✔	✔	
Cochrane Database of Systematic Reviews - Cochrane Library CD-ROM	✔		✔	
Controlledtrials.com http://www.controlledtrials.com/		✔		
Database of Abstracts of Reviews of Effectiveness (DARE) http://nhscrd.york.ac.uk/	✔		✔	
DH-Data - SilverPlatter		✔	✔	✔
EconBase http://www.elsevier.com/homepage/sae/ econbase/menu.sht				✔
EconLit - SilverPlatter				✔
EMBASE - SilverPlatter	✔	✔	✔	
HELMIS - SilverPlatter		✔	✔	✔
HTA database http://nhscrd.york.ac.uk/	✔			✔
Index to Scientific and Technical Proceedings - Web of Science		✔	✔	
King's Fund Database - SilverPlatter		✔	✔	✔
Martindale Pharmacopoiea - DataStar			✔	
MEDLINE - SilverPlatter	✔	✔	✔	
National Research Register - CD-ROM		✔		
NHS Economic Evaluation Database http://nhscrd.york.ac.uk/				✔
OHE Health Economic Evaluations Database - CD-ROM				✔
PsycLit - SilverPlatter	✔	✔	✔	
Science Citation Index - Web of Science		✔	✔	
Social Science Citation Index - Web of Science		✔	✔	
TOXLINE http://toxnet.nlm.nih.gov/cgi-bin/ sis/htmlgen?TOXLINE			✔	

9.2.2.1 Internet searches

In addition to the databases listed above, general searches of the Internet were undertaken using the search engines *google.com* (http://www.google.com), *Metaeureka* (http://www.metaeureka.com/) and *Altavista* (http://uk.altavista.com/).

The GlaxoSmithKline web site (http://www.gsk.com/) was searched for relevant product information.

RxList (http://www.rxlist.com) and the *British National Formulary 41* (http://www.bnf.vhn.net/) were searched for pharmacology, dosage and clinical indications information.

The Medicines Control Agency website (http://www.mca.gov.uk/index.htm), the Committee on Safety of Medicines website (http://www.mca.gov.uk/aboutagency/regframework/csm/csmhome.htm) and the Drug and Therapeutic Bulletins website (http://www.which.net/health/dtb/main.html) were searched for safety information.

In all cases, due to the basic search facilities of each website it was not possible to conduct a full search, as outlined below, therefore search terms were kept to a minimum and only the key terms listed below were used:
zyban
amfebutamone
bupropion
wellbutrin
nrt
nicotine

Search results were sifted by hand.

9.2.3 SEARCH STRATEGIES

9.2.3.1 Systematic Review Searches

Literature searches for systematic reviews were conducted in order to identify existing reviews of the effectiveness of bupropion and nicotine replacement therapy in smoking cessation.

The administrative database for DARE was searched rather than the public (Internet-based) version, in order to retrieve details of systematic reviews which did not meet the quality inclusion criteria for the database.

Cochrane Database of Systematic Reviews – CD-ROM
Cochrane Library 2001 Issue 2. Searched 03/05/01

bupropion:me
zyban
amfebutamone
bupropion
buproprion
wellbutrin
#1 or #2 or #3 or #4 or #5 or #6
smok* or tobacco or nicotin*
#7 and #8
nicotine next replacement next therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#9 or #10 or #11 or #12

Database of Abstracts of Reviews of Effectiveness (DARE). Administrative database
Searched 03/05/01
Health Technology Assessment (HTA) Database. Public version
Searched 03/05/01

bupropion/subject heading
zyban/all fields
amfebutamone/all fields
bupropion/all fields
buproprion/all fields
wellbutrin/all fields
#1 or #2 or #3 or #4 or #5 or #6
(smok* or tobacco or nicotin*)/all fields
#7 and #8
nicotine replacement therap*/all fields
nrt/all fields
nicotin*(5w)(patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#9 or #10 or #11 or #12

The following databases were searched from 2000 onwards in order to identify any existing systematic reviews which had not yet been included on the DARE database of systematic

reviews. These databases are regularly searched for reviews for inclusion in DARE, however due to the appraisal process there may be some delay in review abstracts becoming publicly available on the database.

MEDLINE (SilverPlatter and PubMed)
2000-May 2001. Searched 03/05/01
SilverPlatter search strategy provided

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
smok* or tobacco or nicotin*
#3 and #4
nicotine replacement therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7 or #8
#5 or #9
review* or overview*
metaanalys*
meta analys*
metanalys*
#11 or #12 or #13 or #14
"Review-Literature"
#15 or #16
#10 and #17
#18 and (PY >= "2000")

CINAHL (SilverPlatter)
2000-February 2001. Searched 03/05/01

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
smok* or tobacco or nicotin*
#3 and #4
nicotine replacement therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7 or #8
#5 or #9
review* or overview*
metaanalys*
meta analys*
metanalys*
"Review-Literature"
"Systematic-Review"/ all topical subheadings / all age subheadings
#11 or #12 or #13 or #14 or #15 or #16
#10 and #17
#18 in ti,ab,de
#19 and (PY >= "2000")

EMBASE (SilverPlatter)
2000-February 2001. Searched 03/05/01

"amfebutamone"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
smok* or tobacco or nicotin*
#3 and #4
nicotine replacement therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7 or #8
#5 or #9
review* or overview*
metaanalys*
meta analys*
metanalys*
"review"/ all subheadings
systematic review* or overview*
#11 or #12 or #13 or #14 or #15 or #16
#10 and #17
#18 and (PY >= "2000")

PsycLit (WebSpirs)
2000-May 2001. Searched 03/05/01

zyban
amfebutamone
bupropion
buproprion
wellbutrin
#1 or #2 or #3 or #4 or #5
smok* or tobacco or nicotin*
#6 and #7
nicotine next replacement next therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#8 or #9 or #10 or #11
review* or overview*
metaanalys*
meta analys*
metanalys*
#13 or #14 or #15 or #16
#12 and #17
#18 and (PY >= "2000")

9.2.3.2 Randomised Controlled Trial Searches

Literature searches were carried out in order to identify randomised controlled trials which had been published too recently to be included in existing systematic reviews. The publication date range was limited to 2000-2001.

Cochrane Controlled Trials Register – CD-ROM
Cochrane Library 2001 Issue 2. Searched 02/05/01
National Research Register – CD-ROM
2001 Issue 1. Searched 03/05/01
(NRR results sifted by hand for RCTs)

bupropion:me
zyban
amfebutamone
bupropion
buproprion
wellbutrin
#1 or #2 or #3 or #4 or #5 or #6
smok* or tobacco or nicotin*
#7 and #8
nicotine next replacement next therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#9 or #10 or #11 or #12

MEDLINE (SilverPlatter and PubMed)
2000-May 2001. Searched 03/05/01
(SilverPlatter search strategy provided)

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
smok* or tobacco or nicotin*
#3 and #4
nicotine replacement therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7 or #8
#5 or #9
pt = "randomized-controlled-trial"
pt = "controlled-clinical-trial"
"Randomized-Controlled-Trials"/ all subheadings
"Random-Allocation"
"double-blind-method"/ all subheadings
"single-blind-method"/ all subheadings
pt = "clinical-trial"
explode "Clinical-Trials"/ all subheadings
(clin* near trial*) in ti,ab
(singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
"Placebos"/ all subheadings

placebo* in ti,ab
random* in ti,ab
"Research-Design"/ all subheadings
"Random-Allocation"
(control* near (trial* or stud*)) in ti,ab,mesh
crossover in ti,ab,mesh
explode "Evaluation-Studies"/ all subheadings
tg=comparative-study
#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
editorial in pt
comment in pt
letter in pt
tg = "animal"
tg = "human"
#34 not (#34 and #35)
#30 not (#31 or #32 or #33 or #36)
#10 and #37
#38 and (py>= "2000")

EMBASE (SilverPlatter)
2000-February 2001. Searched 02/05/01

"amfebutamone"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
smok* or tobacco or nicotin*
nicotine replacement therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
(#1 or #2) and #3
#4 or #5 or #6
#7 or #8
"randomized-controlled-trial"/ all subheadings
"randomization"/ all subheadings
"double-blind-procedure"/ all subheadings
"single-blind-procedure"/ all subheadings
"crossover-procedure"/ all subheadings
explode "clinical-trial"/ all subheadings
clin* near trial*
(singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
"placebo"/ all subheadings
placebo* in ti,ab
random* in ti,ab
control* near (trial* or stud*)
crossover
rct*
#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#9 and #24
#25 and (py>= "2000")
explode "animal"/ all subheadings
explode "human"/ all subheadings

#27 not (#27 and #28)
#26 not #29

PsycLit (WebSpirs)
2000-May 2001. Searched 03/05/01
HELMIS (SilverPlatter)
2000-1998. Searched 03/05/01
DH-Data (SilverPlatter)
2000-February 2001. Searched 03/05/01
King's Fund Database (SilverPlatter)
2000- February 2001. Searched 03/05/01
CancerLit (SilverPlatter)
2000-March 2001. Searched 03/05/01

zyban
amfebutamone
bupropion
buproprion
wellbutrin
#1 or #2 or #3 or #4 or #5
smok* or tobacco or nicotin*
#6 and #7
nicotine next replacement next therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#8 or #9 or #10 or #11
clin* near trial*
(singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
placebo* in ti,ab
random* in ti,ab
control* near (trial* or stud*)
crossover
rct*
#13 or #14 or #15 or #16 or #17 or #18 or #19
#12 and #20
#21 and (py>= "2000")

CINAHL (SilverPlatter)
2000-February 2001. Searched 02/05/01

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
smok* or tobacco or nicotin*
#3 and #4
nicotine replacement therap*
nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7 or #8
#5 or #9
explode "Clinical-Trials"/ all topical subheadings / all age subheadings

randomi?ed near2 (trial* or stud*)
placebo*
(doubl* or singl* or trebl* or tripl*) near2 (blind* or mask*)
rct*
exact{clinical-trial} in dt
clin* near trial*
"Placebos"/ all topical subheadings / all age subheadings
control* near (trial* or stud*)
crossover
#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#10 and #21
#10 in ti,ab,de
#21 in ti,ab,de
#23 and #24
#25 and (py >= "2000")

Science Citation Index (Web of Science)
2000-May 2001. Searched 03/05/01
Social Science Citation Index (Web of Science)
2000-May 2001. Searched 03/05/01
Index to Scientific and Technical Proceedings (Web of Science)
2000-May 2001. Searched 03/05/01
Biosis (Edina)
2000-May 2001. Searched 03/05/01

(((bupropion or zyban or amfebutamone or buproprion or wellbutrin) and (smok* or tobacco or nicotin*)) or nicotine replacement therapy or nrt or (nicotin* and (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*))) and (rct* or random* or placebo* or blind* or control*)

Controlledtrials.com (http://www.controlledtrials.com)
2000-May 2001. Searched 03/05/01

bupropion or zyban or amfebutamone or buproprion or wellbutrin
smok* or tobacco or nicotin*
#1 and #2
nicotine replacement therapy or nrt
nicotin* and (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#3 or #4 or #5

9.2.3.3 Adverse Effects Searches

Literature searches for the adverse effects and safety of bupropion and NRT were designed to retrieve only trials wherever possible. However, some databases cannot be reliably restricted by study type, and in these cases the search was not limited by study design, and the results of the searches were sifted by hand.

An additional set of searches was carried out to identify any systematic reviews on the adverse effects and safety of bupropion/NRT. This search was only conducted on databases of systematic reviews (DARE and the Cochrane Database of Systematic Reviews), and on databases on which search strategies had previously been limited by study type (i.e.

MEDLINE and EMBASE). The administrative database of DARE was searched rather than the public (Internet-based) version, in order to retrieve details of systematic reviews which did not meet the quality inclusion criteria for the database

These searches were designed to retrieve all references on the adverse effects of bupropion, and were not limited to its use in smoking cesstion.

The search strategy was amended following comments from the review team, and additional terms were added.

Databases were searched from the date of inception to the most recent date available.

MEDLINE (SilverPlatter)
1966 – Dec 2000. Searched 09/04/01

RCT search:

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
side effect* or safety
adverse near3 (effect* or reaction* or event*)
#4 or #5
#3 and #6
"Bupropion"/ adverse-effects
#7 or #8
nicotine replacement therapy or nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#10 or #11
#12 and #6
#9 or #13
explode "Epidemiologic-Studies"/ all subheadings
explode "Clinical-Trials"/ all subheadings
#15 or #16
#14 and #17

Systematic Review search:

"Bupropion"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
side effect* or safety
adverse near3 (effect* or reaction* or event*)
#4 or #5
#3 and #6
"Bupropion"/ adverse-effects
#7 or #8
nicotine replacement therapy or nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#10 or #11
#12 and #6
#9 or #13

review or overview
data synthesis
published studies in ab
data extraction in ab
"Meta-Analysis"
meta analysis in ti
comment in pt
letter in pt
editorial in pt
animal in tg
human in tg
#24 not (#24 and #25)
#14 not (#21 or #22 or #23 or #26)
#15 or #16 or #17 or #18 or #19 or #20
#27 and #28

EMBASE (SilverPlatter)
1980 – Feb 2001. Searched 09/04/01

RCT search:

"amfebutamone"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
(side effect* in ti,ab) or safety
adverse near3 (effect* or reaction* or event*)
#4 or #5
#3 and #6
"amfebutamone"/ adverse-drug-reaction
#7 or #8
nicotine replacement therapy or nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#10 or #11
#12 and #6
#9 or #13
explode "Clinical-Study"/ all subheadings
#14 and #15

Systematic review search:

"amfebutamone"/ all subheadings
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
(side effect* in ti,ab) or safety
adverse near3 (effect* or reaction* or event*)
#4 or #5
#3 and #6
"amfebutamone"/ adverse-drug-reaction
#7 or #8
nicotine replacement therapy or nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#10 or #11

#12 and #6
#9 or #13
metaanalys*
meta analys*
metanalys*
systematic review*
#15 or #16 or #17 or #18
#14 and #19

CINAHL (SilverPlatter)
1982 – Dec 2000. Searched 09/04/01

"Bupropion"/ all topical subheadings / all age subheadings
(zyban or amfebutamone or bupropion or buproprion or wellbutrin) in ti,ab,de
#1 or #2
(side effect* or safety) in ti,ab,de
(adverse near3 (effect* or reaction* or event*)) in ti,ab,de
#4 or #5
#3 and #6
"Bupropion"/ adverse-effects / all age subheadings
#7 or #8
nicotine replacement therapy or nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#10 or #11
#12 and #6
#9 or #13

HELMIS (SilverPlatter)
1984-1998. Searched 09/04/01
DH-Data (SilverPlatter)
1983-February 2001. Searched 09/04/01
King's Fund Database (SilverPlatter)
1979-February 2001. Searched 09/04/01
AMED (SilverPlatter)
1985-Dec 2001. Searched 09/04/01
PsycLit (WebSpirs)
1969-Apr 2001. Searched 17/04/01

zyban or amfebutamone or bupropion or buproprion or wellbutrin
adverse near3 (effect* or reaction* or event*)
side effect* or safety
#2 or #3
#1 and #4
nicotine replacement therapy or nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7
#8 and #4
#5 or #9

Science Citation Index (Web of Science)

1981-Apr 2001. Searched 09/04/01
Social Science Citation Index (Web of Science)
1981-Apr 2001. Searched 09/04/01
Index to Scientific and Technical Proceedings (Web of Science)
1990-Apr 2001. Searched 09/04/01
Biosis (Edina)
1993-Apr 2001. Searched 09/04/01

(bupropion or zyban or amfebutamone or buproprion or wellbutrin or nrt or nicotine replacement therapy or (nicotin* and (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*))) and (side effect* or (adverse and (effect* or reaction* or event*)) or safety)

Cochrane Controlled Trials Register – CD-ROM
Cochrane Library 2001 Issue 2. Searched 09/04/01

zyban or amfebutamone or bupropion or buproprion or wellbutrin
(side next effect*) or safety
adverse near (effect* or reaction* or event*)
#2 or #3
#1 and #4
(nicotine next replacement next therapy) or nrt
(nicotine near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#6 or #7
#4 and #8
#5 or #9

Toxline (Dialog)
1965-Apr 2001. Search 09/04/01
MEDLINE duplicates removed in line #11

s bupropion or zyban or amfebutamone or buproprion or wellbutrin
s side(w)effect? or safety
s adverse(5w)(effect? or reaction? or event?)
s s2 or s3
s s1 and s4
s nicotine(w)replacement(w)therapy or nrt
s nicotine(5w)(patch? or gum or inhaler? or spray? or tablet? or transdermal or lozenge?)
s s6 or s7
s s4 and s8
s s5 or s9
s s10/nonmed

Martindale Pharmacopoeia (Datastar)
32nd Edition (April 1999) most recent available. Searched 18/04/01

bupropion or zyban or amfebutamone or buproprion or wellbutrin
side adj effect$ or safety
(adverse near (effect$ or reaction$ or event$)).rf.

2 or 3
1 and 4
nicotine adj replacement adj therapy or nrt
nicotine near (patch$ or gum or inhaler$ or spray$ or tablet$ or transdermal or lozenge$)
6 or 7
4 and 8
5 or 9

Database of Abstracts of Reviews of Effectiveness (DARE). Administrative database
Searched 09/04/01

Bupropion/subject heading
(zyban or amfebutamone or bupropion or buproprion or wellbutrin)/all fields
#1 or #2
(side effect* or safety)/all fields
(adverse(3w)(effect* or reaction* or event*))/all fields
#4 or #5
#3 and #6
(nicotine replacement therapy or nrt)/all fields
(nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*))/all fields
#8 or #9
#10 and #6
#7 or #11

Cochrane Database of Systematic Reviews – CD-ROM
Cochrane Library 2001 Issue 2. Searched 09/04/01

bupropion:me
zyban or amfebutamone or bupropion or buproprion or wellbutrin
#1 or #2
side effect* or safety
adverse near (effect* or reaction* or event*)
#4 or #5
#3 and #6
nicotine replacement therapy or nrt
nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
#8 or #9
#10 and #6
#7 or #11

9.2.3.4 Cost-Effectiveness Searches

Searches were carried out on a range of specialist economic evaluation databases in order to identify any records which had not been retrieved by previous searches of general databases. The searches were not limited by study type, and all databases were searched from date of inception to the most recent date available.

HELMIS, the King's Fund Database and DH-Data were searched to identify any additional specifically UK-based cost-effectiveness data. The administrative database for NHS EED

was searched rather than the public (Internet-based) version, in order to retrieve details of economic evaluations which did not meet the quality inclusion criteria for the database.

NHS Economic Evaluation Database (NHS EED). Administrative database
Searched 18/05/01

s zyban or bupropion or wellbutrin or amfebutamone or buproprion
s nicotine(w)replacement(w)therap$ or nrt
s nicotine(3w)(patch$ or gum or inhaler$ or spray$ or tablet$ or transdermal or lozenge$)
s s1 or s2 or s3

Health Technology Assessment (HTA) Database. Public database
Searched 18/05/01

(zyban or bupropion or wellbutrin or amfebutamone or buproprion)/all fields
(nicotine(w)replacement(w)therap$ or nrt)/all fields
(nicotine(3w)(patch$ or gum or inhaler$ or spray$ or tablet$ or transdermal or lozenge$))/all fields
1 or 2 or 3
cost$ or econom$ or pharmacoeconom$ or price$ or pricing
4 or 5

Health Economic Evaluations Database (HEED). CD-ROM produced by the Office of Health Economics (OHE).
Searched 18/05/01
EconBase. Web interface (http://www.elsevier.com/homepage/sae/econbase/menu.sht)
Searched 18/05/01

zyban or bupropion or wellbutrin or amfebutamone or buproprion or nicotine replacement therapy or nrt or nicotine patch or nicotine patches or nicotine gum or nicotine inhaler or nicotine inhalers or nicotine spray or nicotine tablet or nicotine tablets or transdermal nicotine or nicotine lozenge or nicotine lozenges

EconLit (SilverPlatter)
1969-March 2001. Searched 18/05/01
HELMIS (SilverPlatter)
1984-1998. Searched 18/05/01
DH-Data (SilverPlatter)
1983-March 2001. Searched 18/05/01
King's Fund Database (SilverPlatter)
1979-March 2001. Searched 18/05/01

zyban or bupropion or wellbutrin
nicotine replacement therap*
nicotine near3 (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
buproprion or amfebutamone
#1 or #2 or #3
#1 or #2 or #3 or #4
cost* or econom* or pharmacoeconom* or price* or pricing

#6 and #7

9.3 LIST OF EXCLUDED STUDIES

Reference	Bupropion or NRT	
Abelin 1989 [218]	NRT	Efficacy study
Addington 1998 [219]	NEITHER	Non-systematic review
Adnot 1998 [220]	NEITHER	Very general review (and French)
Ahluwalia 1998 [221]	NRT	Efficacy
Ajac 1983 [222]	BUPROPION	Efficacy study
Alsagoff 1993 [223]	NRT	General review
Andersen 1999 [224]	NEITHER	Not about NRT of bupropion
Andolsk 1997 [225]	NRT	Not original article see
Anon 1991 [226]	BUPROPION	Not original article see [170]
Anon 1991 [227]	BUPROPION	Not original article see [153]
Anon 1994 [228]	NRT	Not original article.
Anon 1994 [229]	NRT	Not original paper see [109]
Anon 1997 [230]	NRT	Not original article
Anon 1997 [231]	NRT	Very brief comment type article. No refs.
Anon 1999 [232]	BUPROPION	Not original article see Hebert 1999
Aparici 1994 [233]	NRT	In Spanish old RCT efficacy
Areechon 1988 [234]	NRT	Efficacy study
Ashenden 1997 [235]	NEITHER	Not specificly related to NRT of bupropion
Balfour 2000 [236]	NRT	Non-systematic review
Barrueco 2001[237]	NRT	Not a direct comparative study of NRT. Also not in English.
Batey 1998 [238]	BUPROPION	Antidepressant efficacy study
Batra 1995 [239]	NRT	German language
Becona 2000 [240]	NEITHER	Focuses on extent and number of publications
Bellos 1991 [241]	NRT	Spanish language review
Benowitz 1988 [242]	NRT	Non-systematic review
Benowitz 1991 [243]	NRT	Brief review
Benowitz 1997 [244]	NRT	Non-systematic review of CV risk with NRT
Blondal 1997 [245]	NRT	Efficacy study
Blondal 1999 [246]	NEITHER	Efficacy study of fluoxetine in smoking cessation
Bohadana 2000 [247]	NRT	Included in the latest update of the Cochrane review of NRT (Ed 3, 2001)
Bolliger 2000 [248]	NEITHER	Non-systematic review
Bolliger 2000 [249]	NRT	Included in the latest update of the Cchrane review of NRT (Ed 3, 2001)
Bonapace 1997 [250]	NRT	Review of efficacy in inflammatory bowel disease
Orja Villegas 1986 [251]	BUPROPION	Review in Spanish
Breckenridge 2001[252]	BUPROPION	Not original data
Brown 2000 [2]	NRT	Non-systematic review
Buchkremer 1988 [253]	NRT	Old efficacy study

Reference	Bupropion or NRT	Reason for exclusion*
Campbell 1996 [254]	NRT	Efficacy study
Canive 1998 [255]	BUPROPION	Efficacy study
Carmody 1988 [256]	NRT	Efficacy study
Cato 1983[257]	BUPROPION	Methodology paper: bupropion used merely as an example
Christen 1988 [258]	NRT	Non-systematic review
Cinciripini 1998 [7]	NEITHER	Non-systematic review
Clemens 1995 [259]	NRT	Efficacy study of NRT on symtpoms of Parkinson's disease.
Clouse 2000 [260]	NRT	Study in dogs
Conners 1996 [261]	NRT	Efficacy in ADHD
Cooper 1994 [262]	NRT	Non-systematic review
Covey 2000 [263]	BUPROPION	Non-systematic review
Croft 1999 [264]	BUPROPION	Primarily an efficacy study
Crowley 1995 [265]	NRT	Efficacy study
Dailey 1996 [266]	BUPROPION	Non-sytematic review. Refs checked.
Dale 1995 [267]	NRT	Efficacy study
Danis 1997 [268]	NEITHER	Non-systematic review
Daughton 1992 [269]	NRT	Efficacy (and in Italian)
David 2001 [270]	NEITHER	Protocol of Cochrane review
Davidson 1983 [271]	BUPROPION	Antidepressant effciacy study
Davidson 1998 [272]	NRT	Old efficacy
de Wit 1995 [273]	NRT	Non-systematic review of abuse potential
Dempsey 2001[274]	NRT	Review of nicotine in pregnancy
Dewan 1999 [275]	BUPROPION	Using PDR data to rank antidepressants not based on real data
Dubois 1999 [276]	NRT	Non-systematic review
Dufresne 1985 [277]	BUPROPION	Primarily an efficacy study
Fabre 1978 [278]	BUPROPION	Efficacy study
Fabre 1983 [279]	BUPROPION	Antidepressant effciacy study
Fagerstrom 1982 [280]	NRT	Efficacy study
Fagerstrom 2000 [281]	NRT	Included in the latest update of the Cochrane review of NRT (Ed 3, 2001)
Fee 1982 [282]	NRT	Efficacy study
Feighner 1984 [283]	BUPROPION	Efficacy study
Feighner 1986 [284]	BUPROPION	Efficacy study
Feighner 1991[284]	BUPROPION	Efficacy study
Ferry 1999 [16]	BUPROPION	Non-systematic review
Finkel 1996 [285]	BUPROPION	Overview of antidepressants
Fiore 1993 [286]	NRT	Same as [103] (and not study)
Fiore 2000 [287]	NRT	This paper based on full report[23]
Fiore 2000 [288]	NRT	Not RCT or safety
Fortmann 1988 [289]	NRT	Efficacy study
Foulds 1993 [290]	NRT	Efficacy study
Frenkel 1992 [291]	BUPROPION	Very general review

Reference	Bupropion or NRT	Reason for exclusion*
Galvin 2001 [292]	NRT	Less than 6 mths follow-up
Gardner 1983 [293]	BUPROPION	Only in depressed pts intolermat of tricyclic antidepressants
Gariti 2000[294]	NRT	No real data
Gentry 2000 [295]	NRT	Not an RCT or AE paper
George 2000[296]	NRT	Not really NRT: compares two forms of councelling in schizophrenia patients
Girdler 1997 [297]	NRT	Not really about NRT but effects of smoking
Glavin 1987 [298]	BUPROPION	Pharmacology
Glover 1997[299]	NRT	Touches on safety of NRT in pts with COPD but primarily efficacy study
Goldstein 1998 [300]	BUPROPION	Non-systematic review
Gonzales 2001 [301]	BUPROPION	Follow-up less than 6 months
Goodnick 1991 [302]	BUPROPION	Old efficacy study
Gore 1998 [303]	NRT	Non-systematic review
Gorman 1997 [304]	NEITHER	Not bupropion or NRT
Gourlay 1995 [305]	NRT	Efficacy study
Gourlay 1996 [9]	NRT	Non-systematic review
Grandes 2000 [306]		Not bupropion or NRt and not RCT
Grossman 1999 [307]	BUPROPION	Old efficacy study
Hajek 1988 [308]	NRT	Not a safety study
Hakek 1999 [309]	NRT	Old efficacy study
Halaris 1983 [310]	BUPROPION	Antidepressant effciacy study
Hamilton 1983 [311]	BUPROPION	Pharmacology only
Hamilton 1998 [312]	BUPROPION	Bupropion just mentioned
Harto Truax 1982 [313]	BUPROPION	Old efficacy study
Harto Truax 1983[314]	BUPROPION	Non-systematic pooling of body weight data from various studies
Hatsukami 2000 [315]	NRT	Not smoking cessation
Haustein 2000 [4]	NRT	Non-systematic review
Hayes 1986 [316]	BUPROPION	Non-systematic review
Hays 1999 [317]	NRT	Old efficacy study
Hays 1999[318]	NRT	Subset of Jorenby 1995[319]
Hays 2001 [320]	NEITHER	Not about NRT of bupropion
Helge 2000 [321]	Both	Non-systematic review
Henningfield 103 [322]	NEITHER	Non-systematic review
Herrera 1995 [323]	NRT	Primarliy an effciacy study
Hilleman 1994 [324]	NRT	Efficacy study
Hjalmarson 1984 [325]	NRT	Old effciacy study
Hjalmarson 1994 [326]	NRT	Old efficacy study
Hjalmarson 1997 [327]	NRT	Old efficacy study
Homsy 1997 [328]	NRT	Pharmacokinetics only
Horne 1988 [329]	BUPROPION	Efficacy study
Hughes 1984 [330]	BUPROPION	Old effciacy study
Hughes 1989 [331]	NRT	Old effciacy study

Reference	Bupropion or NRT	Reason for exclusion*
Hughes 1993 [332]	NRT	Letter (comments)
Hughes 1993 [333]	NRT	Non-systematic review
Hughes 1999 [334]	NRT	Old efficacy study
Hurt 1990 [335]		Efficacy study
Hurt 1994 [336]	NRT	Mainly efficacy study
Hurt 1997 [49]	BUPROPION	Old efficacy
Hurt 2000 [337]	NRT	Efficacy study but not an RCT
ICRF general Practice Research group 1993 [338]	NRT	Old efficacy study
Jacobson 1994[339]	BUPROPION	Not a relevant population
Jarvis 1982 [340]	NRT	Old efficacy study
Jensen 1990 [341]	NRT	Mainly efficacy study
Jimenez Ruiz 1994 [342]	NRT	Not safety
Jimenez Ruiz 1996 [343]	NRT	Old efficacy and in Spanish
Jimenez Ruiz 1997 [344]	NRT	Not primarily AE
Jimenez Ruiz 1999 [345]	NRT	Old efficacy study
Jimenez Ruiz 2000 [346]	NRT	Old efficacy and not RCT (note same ref as[347]
Jimenez-Ruiz 2000 [347]	NRT	Not an RCT (note sme ref as [346]
Johnston 1986[348]	BUPROPION	Just discussion
Jorenby 1995 [319]	NRT	Old efficacy study
Jorenby 1995 [349]	NRT	Non-systematic review
Jorenby 1996 [350]	NRT	About withdrawal symptoms not new effciacy or safety
Jorenby 1999 [39]	BUPROPION	Old efficacy study
Kalman 1998 [351]	NEITHER	Non-systematic review and not specifically relevant
Kane 1983 [352]	BUPROPION	Efficacy study of only 38 pts
Kavoussi 1997 [353]	BUPROPION	Primarily an efficacy study
Kellner 1994 [354]	BUPROPION	Does not report an adverse event
Killen 1999 [355]	NRT	Not safety
Killen 2000 [356]	NRT	NRT included in all treatments therefore not compared with anything
Kinnell 2001 [357]	BUPROPION	Letter –comment
Kirksey 1983 [358]	BUPROPION	Primarily efficacy
Kirksey 1984 [359]	BUPROPION	Title safety and efficacy but study is primarily an effciacy study, there fore exclude.
Kochak 1992 [360]	NRT	Sub-clinical doses
Kornitzer 1995 [361]	NRT	Primarily an efficacy study
Kupecz 1996 [362]	NRT	Efficacy study
Kwan 2001[363]	BUPROPION	Not English language
Labbate 1999 [364]	BUPROPION	Very brief review
Lagrue 1993[365]	NRT	It is a letter commenting on a case report
Lancaster 1998 [14]	NRT	Only includes one or two relevant studies therefore decided to use those rather than review
Lancaster 2001	NRT	Includes studies of NRT versus NRT plus self help interventions, but not motivational support.
Leigh 2001 [366]	NRT	Follow-up less than 6 months
Leischow 1997 [367]	NRT	Withdrawal symptoms

Reference	Bupropion or NRT	
Levin 1994 [368]	NRT	Efficacy study
Lewis 1998 [369]	NRT	Primarily effciacy
Lineberry 1990 [370]	BUPROPION	Efficay study
Lockhart 2000 [371]	NEITHER	About smoking cessation and reducing Mis
Lopez-Arrieta 2001 [372]	NRT	Indication not relevant
Lumley 1999[373]	NRT	Not NRT or bupropion
Margolin 1990 [374]	BUPROPION	Efficacy study
Margolin 1995 [375]	BUPROPION	Cocaine dependence
Martin 1995 [376]	NRT	Primarily an efficacy paper. Adverse events reported very briefly
Martin 1996 [377]	NRT	An RCT with adverse events described for just the treatment arm, and does not distinguish between patch use with and without smoking
Martin 2000 [378]	NEITHER	Description of study
Masco 1994 [379]	BUPROPION	Old efficacy
Matsushima 1995 [380]	NRT	Animal study
Mcgovern 1992 [381]	NRT	Efficacy study
McNabb 1982 [382]	NRT	Pharamcokinetics
Mendels 1983 [383]	BUPROPION	Antidepressant effciacy study
Meredith 1983 [384]	BUPROPION	Antidepressant effciacy study
Mielke 1997 [385]	NEITHER	Non-systematic review
Mintz 1991 [386]	NRT	Primarily interested in effects of alcohol on effectiveness of NRT gum
Mittman 1999 [387]	BUPROPION	Not specific to bupropion
Montalto 1998 [388]	NRT	Clinical practice exercise paper
Montoya 1995 [389]	BUPROPION	Small efficacy study
Moxham 2000 [390]	NEITHER	Editorial comment - background info
Murray 1999 [391]	NEITHER	Non-systematic review
Murray 2000[392]	NRT	NRT not the main difference between treatments
Namerow 1999[393]	BUPROPION	Letter commenting on case report
NHS CRD 1998 [1]	NEITHER	Non-systematic review
Norman 1984 [394]	BUPROPION	General overview of antidepressants
Odishaw 2000 [395]	BUPROPION	Pharmacokinetic Drug Interaction
O'Hara 1993 [396]	NRT	No safety information re NRT
Okuyemi 2000 [397]	NRT	Non-systematic review
Oliver 1993 [398]	BUPROPION	Overview
Orleans 1994 [399]	NRT	Not safety
Othmer 1983 [400]	BUPROPION	Safety not primary objective of study
Patel 2000 [401]		Non-systematic review
Patten 2000 [402]	NRT	Non-systematic review
Patten 2000 [403]	NRT	Follow-up less than 6 months
Pearlstein 1997 [404]	BUPROPION	Efficacy in PMS
Perkins 1996 [405]	NRT	Efficacy study
Perkins 2001 [406]	BOTH	Non-systematic review: useful for background
Perng 1998 [33]	NRT	Old efficacy study

Reference	Bupropion or NRT	Reason for exclusion*
Piasecki 1998 [407]	NRT	Study of withdrawal patterns
Pickworth 1986 [408]	NRT	Pharmacology
Pisinger 1999 [3]	NRT	Non-systematic review
Pitts 1983 [409]	BUPROPION	Antidepressant effciacy study
Preskorn 1984 [410]	BUPROPION	Non-systematic review
Preskorn 1995 [411]	BUPROPION	Source of data for bupropion looks a bit dubious
Ramasubbu 1999 [412]	NEITHER	Not bupropion or NRT
Raw 1980 [413]	NRT	NRT vs psychological therapy BUT not an RCT
Reimherr 1998 [414]	BUPROPION	Primarily an effciacy study
Remick 1982 [415]	BUPROPION	Not safety
Rennard 2000 [416]	NEITHER	Non-systematic review
Rennard 2001 [417]	BUPROPION	No results presented
Richmond 1994 [418]	NRT	Efficacy study
Richmond 1997 [419]	NRT	Non-systematic review
Richmond 1999 [420]	NEITHER	Non-systematic review
Riggs 1998 [421]	BUPROPION	Effiacy in ADHD
Ritvo 1997 [422]	Both	Non-systematic review
Rose 1985 [423]	NRT	Efficacy study
Rose 1990 [424]	NRT	Efficacy study
Rose 1991 [425]	NEITHER	Non-systematic review
Rose 1998 [426]	NRT	NRT vs mecamylamine but only as pre-cessation tretament
Rose 1999 [427]	NEITHER	Not mecamylamine versus NRT
Rosenstein 1993 [428]	BUPROPION	Not really about bupropion
Rudorfer 1991 [429]	BUPROPION	Pharmacology
Rudorfer 1994 [430]	BUPROPION	Too general
Russell 1993 [431]	NRT	Old efficacy
Sachs 1993 [432]	NRT	Old effciacy study
Sachs 1994 [433]	BUPROPION	Efficacy study
Saenghirunvattana 1995 [434]	NRT	Efficacy study
Salin-Pascual 1995 [435]	NRT	Effects of nicotine on sleep in patients with depression. Not realy Aes or safety
Salvador Livina 1987 [436]	NRT	Old efficacy study
Sampablo Lauro 2000 [437]	NRT	Efficacy study
Sarko 2000 [438]	BUPROPION	Too general
Sawe 1997 [439]	NRT	Just short version of details in the CEASE trial full publication, which is an efficacy study .
Schneider 1995 [440]	NRT	Old efficacy study
Schneider 1996 [441]	NRT	Old efficacy study
Selby 2001 [442]	BUPROPION	Follow-up less than 6 months
Semenchuk 2000 [443]	BUPROPION	Efficacy fo bupropion in neuropathic pain
Settle 1998[444]	BUPROPION	Non-systematic review of side effect profile of bupropion
Settle 1999 [445]	BUPROPION	Excluded as no real explanation of reason for selecting these 3 studies for pooling.
Shaw 1998 [446]	NRT	Not a safety study

Reference	Bupropion or NRT	Reason for exclusion*
Shiffman 2000 [447]	NRT	Outcome effect on morning craving and follow-up less than 6 months
Shiffman 2000 [448]	NRT	Follow-up less than 6 months
Shopsin 1983 [449]	BUPROPION	Old efficacy study
Shuster 1997 [450]	NRT	Not original article
Shuster 1997 [451]	NRT	Not original article - newspaper like report
Silagy 2001 [452]	NEITHER	Not relevant to NRT or bupropion
Silver 1996 [453]	NRT	Efficacy with neuroleptics in Tourette's syndrome
Sinusas 1993 [454]	NRT	Old efficacy study
Sivyer 1994 [455]	NRT	Efficacy study
Skaar 1997 [6]	NEITHER	Non-systematic review
Smith 1992 [456]	NRT	A non-systematic review of skin reactions and causes
Smith 1995 [457]	NRT	Old efficacy study
Smith 1996 [458]	NRT	Primarily efficacy study
Sonderskov 1997 [459]	NRT	Primarily efficacy study
Spencer 1993[460]	BUPROPION	Not a relevant population
Spiller 1994 [461]	BUPROPION	Bupropion overdose –not relay applicacble to normal use of drug
Stapleton 1995 [201]	NRT	Old efficacy study
Stead 2001 [462]	NEITHER	Not relevant
Stern 1982 [463]	BUPROPION	Two studies both efficacy
Stoll 1994 [464]	BUPROPION	Not really about effects of bupropion
Strecher 1999 [465]	NEITHER	Not about bupropion or NRT
Sudan 1994 [466]	NRT	Discussion paper
Sudan 1995 [467]	NRT	Discussion paper
Sutherland 1992 [468]	NRT	Old efficacy study
Tennstedt 1998 [469]	NRT	Review (in French) of transdermal preparations - not sp. NRT
Thomas 1995 [470]	NRT	Efficacy in ulcerative colitis
Thompson 1998 [8]	NRT	Non-systematic review
Thornton 1986 [471]	NRT	No results
Thorsteinsson 2001[472]	NRT	Follow-up period too short
Tonnesen 1988 [473]	NRT	Efficacy study
Tonnesen 1991 [474]	NRT	Old effciacy study: safety not realy a primary objective
Tonnesen 1992 [475]	NRT	Mainly efficacy study
Tonnesen 1993 [476]	NRT	Old efficacy study
Tonnesen 1993 [477]	NRT	Old efficacy study
Tonnesen 1996 [478]	NRT	Efficacy study
Tonnesen 1999 [119]	NRT	Efficacy study
Tonnesen 1999 [479]	NRT	Non-systematic review
Tonnesen 2000 [34]	NRT	In 2001 update of Silagy (Cochrane review of NRT)
Toral 1998 [480]	NRT	Efficacy (and in Spanish) study
Transdermal Nicotine Study group 1991 [481]	NRT	Efficacy study
Trappler 2000 [482]	BUPROPION	Report of a possible drug interaction (with amantadine)

Reference	Bupropion or NRT	Reason for exclusion*
Tsoh 1997 [483]	NEITHER	Non-systematic review
Tsoh 2000 [484]	NEITHER	Study into incidence of depression after attempting to stop smoking
Tucker 1983 [485]	BUPROPION	Preclinical safety
van den Berkmortel 2000 [486]	NEITHER	Non-systematic review
van der Klauw 1994 [487]	NRT	Eclude - in Dutch
van Ree 1984 [488]	NRT	Efficacy study. Not English
Vida 1999 [489]	BUPROPION	Methodology paper about how to compare AERs from different trials on different drugs. No raw data.
Vieregge 2000 [490]	NRT	Follow-up less than 6 months
Vleggaar 2000 [491]	NRT	Study of effciacy in sclerosing cholangitis
Wallstrom 2000 [492]	NRT	Included in the latest update of the Cchrane review of NRT (Ed 3, 2001)
Walsh 1994 [493]	NEITHER	Exclude but use as background re adverse effects of smoking in pregnancy
Wadland 2001 [494]	NRT	Study of efficacy of telephone counselling when used in addition to usual care (mainly but not exclusively NRT patches)
Weihs 2000 [495]	BUPROPION	Efficacy study
Weiner 2001 [496]	BUPROPION	Not an RCT nor safety study
Weisler 1994 [497]	BUPROPION	Efficacy study
Wenger 1983 [128]	BUPROPION	Non-systematic review
West 1998 [498]	NRT	Comparison with dextrose but follow-up period too short (< 6 months)
West 2000 [499]	NRT	Follow-up less than 6 months
Westman 1993 [500]	NRT	Efficacy study
Westman 1995 [501]	NRT	Efficacy study
Wewers 1999 [502]	NEITHER	Non-systematic review
White 1999 [503]	BUPROPION	Description of data collection but no data
Whiteman 1982 [504]	BUPROPION	Efficacy in depression study
Wilson 1995 [505]	NRT	Efficacy in Alzheimer's Disease
Wilson 2000 [506]		Not about intervention
Wolf 1998 [507]	NRT	Non-systematic review of skin reactions to NRT patches
Wong 1999 [508]	NRT	Effects on gastric emptying
Wongwiwatthananukit 1998 [509]	Both	Non-systematic review
Zajecka 2001 [510]	BUPROPION	Non-systematic review
Zhu 2000 [511]	NRT	Not RCT and not realy about NRT and not safety
Zobrist 19 [512]	NRT	Mainly efficacy
Zobrist 1996 [513]	NRT	Pharmacokinetics
Zung 1983 [514]	BUPROPION	Efficacy study

* 'Efficacy study' or 'old efficacy' indicates that study is primariliy about efficacy and is not newly identified for this review, having been included in previous systematic reviews

9.4 DATA EXTRACTION FORMS

9.4.1 Data Extraction from Systematic Reviews

Data was extracted from Systematic Reviews and entered into an ACCESS database under the following headings:

Review details
Endnote reference
Author (e.g. Jones et al.)
Date i.e. year of publication
Name of review
Objective of review
Inclusion criteria of SR (study design, participant details, intervention, outcomes)
Exclusion criteria
How quality of studies assessed
Number of studies included in SR
Types of studies and number included in the review {RCTs, Quasi-RCTs, controlled-trials, other}
Participants included in review (type of smokers, prportion of male/female, level of nicotine dependance, Fagerstrom score)
Specific intervention
Specific comparator
Definition of cessation used
Duration of follow-up
Setting (hospital, general practice, smoking clinic, other)
Participants actually included
Outcome measure (s) {description including definition of cessation used (point prevalence or sustained abstinence or other)
Quality of studies in SR
Comments

Results of review
Comparison (describe comparison: which intervention(s) versus which comparators, nature of sub-group if any)
Number of studies included in the comparison
Comments on design and quality of studies included in the comparison
Pooled Odds ratio or RR with 95% CI for comparison 1 {insert data}
Other result(s) for comparison 1
Comment on result of comparison 1
Repeat for all comparisons

9.4.2 Data Extraction of Effectiveness data

Effectiveness data will be extracted from newly identified RCTs only and entered into an Access database under the following headings: these data will not duplicate those extracted from systematic reviews

Study Details
Endnote reference Primary source (database, handsearching, company submission)
Author (e.g. Jones et al)
Date (i.e. year of publication or year of interim data collection)
Type of report (abstract, full manuscript, interim report)
Type of study phase (phase II, III, IV or not stated)
Level of randomisation (patient or therapist)

Length of follow-up period
Number and times of follow-up measurements
Outcome measures
Definition of cessation used
Method of assessment of cessation of smoking
Intention to treat analysis performed (yes, no, not stated, unclear)
Per protocol analysis performed (yes, no, not stated, unclear)
Participants details

Specific Intervention(s)
Specific comparator(s)
Number of participants recruited and attrition

Study quality
Check list given in Appendix 9.5

Results
Percentage not smoking at 3 months, 6 months and 12 months with intervation and comparator.
Result for comparison (odds ration with 955 Confidence Intervals).

9.4.3 Data Extraction of adverse events data

Adverse event data will be extracted and entered into an Access database under the following headings:

Nature of data (AE search, RCT search, other)
Endnote reference
Author (e.g. Jones et al)
Date (i.e. year of publication or year of interim data collection)
Design of stduy
Specific intervention
Specific comparator
Duration of therapy
Duration of follow-up
Participants' details
List all adverse events associated with intervention
Proportion of participants experiencing any adverse event
Clinical significance of this adverse event
Comments on adverse event
Repeat for all adverse events reported

9.4.4 Data extraction sheet for studies of economic evaluation of smoking cessation interventions

1. Study details Author: _____

Title: _____

Source: _____

Year: _____ Country: _____

2. Interventions compared

1) _____

2) _____

3) _____

4) _____

3. Participants (inclusion criteria):

_____

4. Outcomes measured

1) Costs 2) Number of quitter 3) Life-years saved
4) QALYs saved 5) Other: _____

5. How effectiveness (quit rate) of interventions established?

1) Individual RCTs 2) Meta-analysis of RCTs 3) Observational studies
4) Other:_____

6. Methods for estimating

1) Spontaneous quitting rate: _____

2) Relapse rate after cessation: _____

3) LFYs or QALYs from number of quitters: _____*:*

7. Categories of costs considered

1) Healthcare costs: _____

_____

2) Patient & family costs: _____
3) Other costs: _____

8. Viewpoints (perspectives) for analysis: _____

9. Rate of discounting: 1) Costs: _____ 2) Health benefits: _____

10. Other important assumptions:

1) _____

2) _____

3) _____

4) _____

11. Dealing with uncertainty: 1) Sensitivity analysis 2) Other: _____

Major Sensitive factors: _____

12. Indirect comparison with other healthcare interventions

1) No 2) If yes, a list of other interventions:

_____ _____

13. Author(s)' conclusions

_____

14. Results (main findings)

1) Absolute value

Intervention	Costs/1,000	No. of quitters per 1,000	LFYs saved per 1,000	QALYs saved per 1,000
1.				
2.				
3.				
4.				

2) Increamental analysis

(Reference intervention: _____)

Intervention	Costs per quitter	Costs per death prevented	Costs per LFYS	Costs per QALYS
1.				
2.				
3.				
4.				

15. Any other relevant information or comments about this study:

9.5 QUALITY ASSESSMENT CRITERIA

The quality of Systematic Reviews was assessed using a check list based on the following criteria (based on the Manual for Selecting Reviews and Writing Abstracts of Reviews for DARE[18]):

Do the inclusion/exclusion criteria for the inclusion of studies in the SR relate to study design, participants, intervention(s) and outcome(s) of interest?
Is there evidence of a comprehensive and inclusive search of the literature, including attempts to identify unpublished studies?
Is the validity of the studies included in the review adequately assessed?
Are the individual studies presented in sufficient detail?
Are the primary studies synthesised appropriately? If a meta-analysis has been performed was heterogeneity tested for adequately?
Have the inclusion/exclusion criteria been applied independently by more than one author?
Have the data been extracted independently by more than one author?
Have the validity criteria been applied independently by more than one author?
Has the validity of the studies been taken into account in the synthesis of the studies?

RCTs of effectiveness were assessed using the following criteria (based on CRD Report No. 4 [19]):

Was the method used to assign participants to the treatment groups really random? (Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)
Was the allocation of treatment concealed? (Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque)
Was the number of participants who were randomised stated?
Were details of baseline comparability presented in terms of nicotine dependence, level of motivation, number of previous attempts to stop smoking and age group (adolescent or adult)?
Were the eligibility criteria for study entry specified?
Were any co-interventions identified that may influence the outcomes for each group?
Were the outcome assessors blinded to the treatment allocation?
Were the individuals who were administered the intervention blinded to the treatment allocation?
Were the participants who received the intervention blinded to the treatment allocation?
Was the success of the blinding procedure assessed?
Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
Were the reasons for any withdrawals stated?
Was an intention to treat analysis included?

Studies of adverse events were assessed using the following criteria:

Systematic reviews and RCTs from which adverse event data are extracted were assessed as described in the previous sections.

Cohort studies and all uncontrolled studies were assessed according to the following criteria (based on the checklists from 'A Pocket Guide to Critical Appraisal' by Iain. K. Crombie 1996 [20]). This checklist was used for cohort studies and for uncontrolled studies because the nature of the questions were deemed appropriate for both types of studies. Clearly, however, a properly conducted cohort study provides a better level of evidence than an uncontrolled study, irrespective of the results of the quality assessment.

Is the group studied clearly stated?
Was there any control group and if not was this appropriate?
Was the follow-up adequate?
Were the aims clearly stated?
Was the study design appropriate?
Was the sample size appropriate?
Were the measurements valid and reliable?
Were the outcome measures appropriate?
Were all participants accounted for?
Were the statistical methods appropriate and well described?

Case-control studies will be assessed according to the following criteria (based on on the checklists from 'A Pocket Guide to Critical Appraisal' by Iain. K. Crombie 1996 [20])

Was the method used for obtaining cases appropriate
Were the controls selected appropriately
Were data collected in the same way for both cases and controls?
Was the follow-up adequate?
Were the aims clearly stated?
Was the study design appropriate?
Was the sample size appropriate?
Were the measurements valid and reliable?
Were the outcome measures appropriate?
Were all participants accounted for?
Were the statistical methods appropriate and well described?
Was there data-dredging?
Was there risk of significant bias?

Survey-type studies will be assessed according to the following criteria (based on on the checklists from 'A Pocket Guide to Critical Appraisal' by Iain. K. Crombie 1996 [20])

Were the aims of the study stated clearly?
Was the population studied appropriate?
Was the size of the population adequate?
Were the statistical methods appropriate and well described?
Was there risk of significant bias?

Surveillance data/ databases

Is the source of the data clearly stated?
Is the population included in the database appropriate?
Are any specific data not included in the database?

Items were graded in terms of yes (item properly addressed), no (item not properly addressed), or unclear or not enough information, or NA not applicable.

9.6 CLINICAL EFFECTIVENESS DATA EXTRACTION TABLES

Appendix 9.6.1 Newly Identified RCTs - NRT

Appendix 9.6.2 Newly Identified RCTs - Bupropion

Appendix 9.6.3 Systematic reviews of effectiveness – NRT

Appendix 9.6.4 Systematic reviews of effectiveness - Bupropion

9.6.1 Newly Identified RCTs - NRT

Study Details	Participant details	Intervention Details	Results	Comments
Clavel-Chapelon 1997[26] **Design of study** Partly blinded, parallel group **Schedule of study visits** Participants were followed-up at day 28 and then every 3 months for the first year and thereafter at 2 years and 4 years **Outcome measures** Smoking cessation **Definition of smoking cessation** Continued abstinence **Method** Self report confirmed by measurement of CO at 4 years	**Inclusion/exclusion** Age 18 or over; smoke at least 10 cigarettes per day. Exclude: History of gastric ulcer; or coronary heart disease or with dental problems; pregnant or lactating women **Baseline characteristics** Sex: 55% Male Mean age: 34 years Mean (SD) age started smoking: 14 (4) years Mean (SD) years smoking: 18 (9) Previous quit attempt: 81% **Participant number and attrition** Total, n=996. gum plus acupuncture, n=268 gum plus placebo acupuncture, n= 213 Placebo gum plus acupuncture, n= 272 Placebo gum plus placebo acupuncture, n = 243 Two participants lost to follow-up after 9 months of study, but ITT analysis was undertaken	**Specific intervention** Nicotine gum 2 mg (ad libitum up to 30 pieces per day during the first 6 months) PLUS acupuncture (days 0, 7 and 28 of study) (G+A) Nicotine gum 2 mg (ad libitum up to 30 pieces per day during the first 6 months) PLUS placebo acupuncture (days 0, 7 and 28 of study) (G+PA) **Comparator** Placebo gum PLUS placebo acupuncture (PG+PA) Placebo gum PLUS acupuncture (days 0, 7 and 28 of study) (PG+A)	**Outcome** Sustained abstinence **% intervention group not smoking % (95% CI)** **at 3 months:** G+A 26.5 (21.2 , 31.8); G+PA 25.8 (19.9, 31.7) **at 12 months:** G+A 11.2 (95% CI 8.0 to 15.5); G+PA 10.9 (7.4 to 15.9) **at 12 months or more:** G+A 6.1 (95% CI 3.7 to 9.9); g+PA 6.2 (95% CI 3.2 to 11.8) **% comparator group not smoking % (95% CI)** **at 3 months:** PG+PA17.7 (13.2,22.2); PG+A 20.6(15.5, 25.7) **at 12 months:** PG+PA 6.5 (4.1, 10.1); PG+A 10.3,(7.1-14.7) **at 12 months or more:** PG+PA 5.1 (3.0,8.5); PG+A 7.3 (4.5, 11.6) **Odds Ratio for comparison** None reported	Log rank test NS for difference beween treatments

Study Details	Participant details	Intervention Details	Results	Comments
Jensen 1991[25] **Design of study** Unblinded, parallel group **Schedule of study visits** Participants attended 8 visits at the clinic each lasting 2 hours. Visits were scheduled at 1, 2, 3, 4, 5, 6, 12 and 26 weeks after the day of quitting **Outcome measures** Smoking abstinence **Definition of smoking cessation** Continued abstinence. Any patient identified as having resumed smoking (CO > 4ppm) at any study visit was not allowed to continue in the study (it was assumed they were counted as treatment failures) **Method** CO monitored (Ecolyser CO-monitor)	**Inclusion/exclusion** Smokers whose daily consumption of cigarettes had been more than 10 for more than 10 years. Exclude: Participants with drug or alcohol misuse, psychiatric problems, cardiovascular disease and pregnant women **Baseline characteristics** Mean (SD) age: 42.1 (12.2). Sex: 219/491 M Mean (SD) age started smoking: 14.8 (2.4) years Mean (SD) daily cigarette consumption: 21.7 (9.1) Mean (SD) Fagerstrom score: 6.3 (2.0) **Participant numbers and attrition** Total, n=496 (only 491 included in demography summary) Silver acetate, n=203 Nicotine gum, n=211 Ordinary gum n=82	**Specific intervention** Nicotine chewing gum (no details of dose or whether 24 or 16 hours) used for three months **Comparator** Siver acetate gum or ordinary chewing gum used for three months	**Outcome measure** Sustained abstinence **% intervention group not smoking at 6 months:** 42.6% **% comparator group not smoking at 6 months:** Silver acetate group 38.9%; ordinary gum 34.2% **Odds ratio for comparison** None reported	No statistically significant difference between treatments for abstinence at 6 months

Study Details	Participant details	Intervention Details	Results	Comments
Wong 1999 [27] **Design of study** Partly blinded (but not for NRT), parallel group **Schedule of study visits** After the initial visit participants returned for visits at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12 following randomisation and then for a final follow-up visit at 6 months post-randomisation **Outcome measures** Smoking cessation **Definition of smoking cessation** One week point prevalence and continued abstinence **Method** For point prevalence participants were considered abstinent from smoking if they reported not smoking in the previous 7 days (confirmed by an expired CO of 8ppm or less). Continued abstinence was defined as no evidence of smoking	**Inclusion/exclusion** Aged 18-65, smoked at least 10 cigarettes per day for the past year, had baseline CO of 15ppm or more, and in good general health Exclude: use of medication contraindicated with NRT or naltrexone,weight less than 100lbs; drug or alcohol abuse; history of depression or other psychiaric disorder requiring medication; cardiovascular, cerebral, respiratory, hepatic, renal or gastrointestinal condition or other systemic disease including cancer. Females who were pregant or at risk of becoming pregnant **Baseline demographics** Mean (SD) age: 42.1 (10.9) years Sex: 53% F Smoked mean (SD) of 27.8 (11.8) cigarettes per day Smoked for a mean (SD) of 24.5 (10.6) years Mean (SD) Fagerstrom score: 7.0 (1.8). Mean (SD) baseline CO levels: 37.5 (15.2) ppm **Participant numbers and attrition** Total, n = 100 Patch plus naltrexone = 26 Patch plus placebo = 25 Naltrexone alone = 23 Placebo alone = 26 For dropouts see comments	**Specific intervention** Nicotine patches (21 mg for 8 weeks followed by 14 mg patches for 4 weeks) Nicotine patches (21 mg for 8 weeks followed by 14 mg patches for 4 weeks) plus naltrexone 50 mg/day **Comparator** Naltrexone 50 mg/day tablet Placebo	**Outcome** Sustained abstinence **% intervention group not smoking at 6 months:** Patch plus placebo 28%; patch plus naltrexone 27% **% comparator group not smoking at 6 months:** naltrexone only 9%; placebo only 8% **Odds Ratio for comparison** OR for patch vs. no treatment 4.26 (95% CI 1.29 to 14.05) OR for naltrexone alone vs. placebo 1.00 (95% CI 0.35 to 2.86)	Thirty-two participants discontinued the study prior to the end of week 12; 20 due to various reasons (e.g. lack of efficacy); 6 lost to follow-up; 3 due to adverse effects; and one due to a protocol violation Subjects receiving naltrexone and those not receiving nicotine patches had higher dropout rates than those on placebo only (p=0.02 and p=0.007)

Study Details	Participant details	Intervention Details	Results	Comments
Wisborg 2000 [29] **Design of study** Double-blind, parallel group **Schedule of study visits** Initial visit prior to woman's 22nd week of pregnancy Second and third visit were scheduled at 8 and 11 weeks after the first visit and the fourth visit was 4 weeks before the expected delivery date **Outcome measures** Smoking cessation **Definition of smoking cessation** Continuous abstinence **Method** Participants were considered continuously abstinent during pregnancy if they were abstinent at the second, third and fourth study visits and had a salivary cotinine level less than 26 ng/ml at the fourth visit	**Inclusion/exclusion** Healthy pregnant women who smoked 10 or more cigarettes per day and were less than 22 weeks pregnant **Baseline characteristics** Mean age: 28 years Mean (SD) consumption of cigarettes per day: nicotine group, 13.4 (4.0); placebo group, 14.2 (4.4) **Participant numbers and attrition** Total, n = 250 Nicotine patch, n=124; Placebo, n=126. Lost to follow-up not reported	**Specific intervention** Nicotine patches (16 hours); 15 mg for 8 weeks and then 10 mg for 3 weeks. Women were also given information, advice and a pamphlet on pregnancy and smoking **Comparator** Placebo patches (16 hours) for 11 weeks. Women were also given information, advice and a pamphlet on pregnancy and smoking	**Outcome** Sustained abstinence **% intervention group not smoking at 6 months:** At fourth pre-natal visit 28% **% intervention group not smoking at 12 months:** At 3 months post-partum 21% **% intervention group not smoking at 12 months or more:** At 12 months post-partum 15% **% comparator group not smoking at 6 months:** At fourth pre-natal visit 25% **% comparator group not smoking at 12 months:** At 3 months post-partum 18% **% comparator group not smoking at 12 months or more:** At 12 months post-partum 14% **Odds Ratio for comparison** None reported	Compliance with study treatment was poor. In the nicotine group only 17% used all the 15 mg patches and 11% used all the 10 mg patches. In the placebo group the proportions were 8% and 7% respectively No statistcially significant difference between the treatment groups for any assessment of smoking cessation

Study Details	Participant details	Intervention Details	Results	Comments
Solomon 2000[28] **Design of study** Unblinded, parallel group **Schedule of study visits** All study 'visits' conducted over the telephone. Assessments conducted at baseline, 10 days and 3 and 6 months after enrolment. **Outcome measures** Smoking cessation **Definition of smoking cessation** Point prevelance (i.e. no smoking in the previous seven days.) **Method** Self reporting. This was confirmed by CO readings in about 60% of reportedly abstinent pts.	**Inclusion/exclusion** Aged 18-50 yrs; smoked more than 4 cigarettes per day, highly motivated to try quitting smoking; were not currently using NRT and had no contraindications to the use of the nicotine patches; were not pregnant or breastfeeding, or planning pregnancy in the next 3 months; low income plus other criteria pertinent to the local conduct of the study. **Baseline characteristics** Mean (SD) age: 33 (8.5) years Mean (SD) cigarettes/day: 23.7 (11.8) **Participant number and attrition** Total, n = 214 5 were withdrawn (two lived in the same household; one became pregnant and two died).	**Specific intervention** Free nicotine patches (for pts smoking more than 10 cigarettes per day: 6 weeks of 21 mg, 2 weeks of 14 mg patches, and 2 weeks 7 mg. For smokers of 5-10 per day: 6 weeks 14 mg, 2 weeks 7 mg only) PLUS proactive telephone support approx biweekly for 3 months. **Comparator** Free nicotine patches (for pts smoking more than 10 cigarettes per day: 6 weeks of 21 mg, 2 weeks of 14 mg patches, and 2 weeks 7 mg. For smokers of 5-10 per day: 6 weeks 14 mg, 2 weeks 7 mg only) WITHOUT proactive telephone support approx biweekly for 3 months.	**Outcome** Point prevelance **% intervention group not smoking % (95% CI)** at 3 months: 42% at 6 months: 23% (20% abstinent at 3 and 6mths) **% comparator group not smoking % (95% CI)** at 3 months: 28% at 6 months: 19% (15% abstinent at both 3 and 6mths) **Odds Ratio for comparison** Not reported	Difference between reported abstinence at 3 mths greater with patch plus telephone support compared to patch alone (p=0.03), but not at 6 months (NS) nor for % quitters at both 3 and 6mths (NS)

Study Details	Participant details	Intervention Details	Results	Comments
GSK 2000[30] * **Design of study** Double-blind, parallel group **Schedule of study visits** Baseline, follow-up (1, 2, 4, 6, 12 weeks, 6 months and 12 months) **Outcome measures** Primary outcome was smoking cessation at 6 weeks. Other outcome measures included smoking cessation at 3, 6, and 12mths, changes in body weight, withdrawal and craving, and adverse events. **Definition of smoking cessation** Maintained abstinence from smoking cigarettes from week 2 to the follow-up point. **Method** Patient self-report verified by exhaled carbon monoxide levels.	**Inclusion/exclusion** **Baseline characteristics** **Participant number and attrition**	**Specific intervention** 2 mg nicotine polacrilex oral lozenge and 4 mg nicotine polacrilex oral lozenge for 6mths **Comparator** 2 mg and 4 mg placebo lozenges	**Outcome** Sustained abstinence	
* The data for this study was supplied by the manufacturer and has had to be removed from this publication for reasons of commercial confidentiality				

Study Details	Participant details	Intervention Details	Results	Comments
GSK 1999[31] * **Design of study** Unblinded, parallel group Schedule of study visits Baseline, weekly visits during the treatment phase (13 weeks) and follow-up evaluations at 6 months and 12 months. **Outcome measures** Primary outcome was continuous smoking abstinence for a 4-wk period beginning with Wk 4 and continuing through the end of Wk 7. Also weekly point prevalence, abstinence from Day 22, changes from baseline cigs/day, severity of nicotine withdrawal symps. **Definition of smoking cessation** Point prevalence defined as continuous abstinence for a 7-day period during the treatment phase and through the 6 mth and 1 yr follow-up. **Method** Subject's report of not smoking (0 cigs/day) comfirmed by CO levels <= 10ppm	**Inclusion/exclusion** **Baseline characteristics** **Participant number and attrition**	**Specific intervention** **Comparator**	**Outcome** Point prevelance	Results reported individually by centre. 6 month data is that reported at Week 26.
* The data for this study was supplied by the manufacturer and has had to be removed from this publication for reasons of commercial confidentiality				

9.6.2 Newly Identified RCTs - Bupropion

Study Details	Participant details	Intervention Details	Results	Comments
GSK 1999 [42] * **Design of study** Double-blind, parallel group **Schedule of study visits** Baseline, treatment visits (up to 7 weeks), monthly follow-up visits from weeks 7 to 52 **Outcome measures** Primary outcome was continuous abstinence from weeks 4-7. However, continuous and point prevalence abstinence was also measured at other follow-up times including weeks 12, 26 and 52. Only abstinence at week 52 is reported in this summary **Definition of smoking cessation** Continuous abstinence was defined as no cigarettes during the defined period. Point prevalence was not defined **Method** Participant self-report confirmed by exhaled carbon monoxide less that 10 parts per million (10ppm)	**Inclusion/exclusion** **Baseline characteristics** **Participant numbers and attrition**	**Specific intervention** Bupropion hydrochloride SR (150 mg bid) for 7 weeks only **Comparator** Placebo	**Outcome 1** Sustained abstinence **Outcome 2** Point prevalence	
* The data for this study was supplied by the manufacturer and has had to be removed from this publication for reasons of commercial confidentiality				

Study Details	Participant details	Intervention Details	Results	Comments
GSK 1999 [31] * **Design of study** Unblinded, parallel group **Schedule of study visits** Baseline, weekly visits during the treatment phase (13 weeks) and follow-up evaluations at 6 months and 12 months **Outcome measures** Primary outcome was continuous smoking abstinence for a 4-wk period beginning with Wk 4 and continuing through the end of Wk 7. Also weekly point prevalence, abstinence from Day 22, changes from baseline cigs/day, severity of nicotine withdrawal symps **Definition of smoking cessation** Point prevalence defined as continuous abstinence for a 7-day period during the treatment phase and through the 6 month and 1 year follow-up **Method** Participants report of not smoking (0 cigs/day) comfirmed by CO levels <= 10ppm	**Inclusion/exclusion** **Baseline characteristics** **Participant numbers and attrition**	**Specific intervention** **Comparator**	**Outcome** Point prevalence	6 month data is that reported at Week 26
* The data for this study was supplied by the manufacturer and has had to be removed from this publication for reasons of commercial confidentiality				

Study Details	Participant details	Intervention Details	Results	Comments
GSK 2000[32] * **Design of study** Double-blind, parallel group **Schedule of study visits** Baseline visit, treatment visits (6 visits) and follow up visits at 12, 26 weeks and 52 weeks **Outcome measures** Primary outcome measure was sustained abstinence at week 7. However, continuous and point prevalence abstinence was also measured at other follow-up times including weeks 12 and 26. Only abstinence at week 26 is reported in this summary **Definition of smoking cessation** Sustained abstinence was a continous absence from smoking for the specified period. Point prevalence was based on abstinence in the previous 7 days **Method** Participant self-report confirmed by exhaled carbon monoxide less than 10 parts per million (10ppm)	**Inclusion/exclusion** **Baseline characteristics** **Participant numbers and attrition**	**Specific intervention** Bupropion hydrochloride SR (150 mg bid) **Comparator** Placebo	**Outcome 1** Sustained abstinence	
* The data for this study was supplied by the manufacturer and has had to be removed from this publication for reasons of commercial confidentiality				

Study Details	Participant details	Intervention Details	Results	Comments
GSK 2001[50] **Design of study** Double-blind, parallel group **Schedule of study visits** Baseline visit, treatment visits (weeks 1-12), follow-up visits (weeks 12, 26 and 52) **Outcome measures** Primary outcome measure was continuous abstinence at week 7. However, continous abstinence, point abstinence, changes in weight, number of cigarettes and adverse events were monitored at weeks 12, 26 and 52 **Definition of smoking cessation** Continuous abstinence was defined as no smoking for the period defined. Point abstinence was defined as no cigarettes in the previous 7 days. **Method** Participant self-report confirmed by exhaled carbon monoxide of less than 10 parts per million (10ppm)	**Inclusion/exclusion** All participants had to have taken and tolerated a 2-week (or longer) course of bupropion for smoking cessation Aged at least 18 years of age; have smoked at least on average 15 cigarettes per day, during the past month; has not quit for more than 24 hours in past month; be motivated to quit smoking. Exclude: Pregnancy; inadequate method of birth control; predisposition to seizures; history or current diagnosis of bulimia or anorexia nervosa; history of severe renal, hepatic, or chronic pulmonary disease; active peptic ulcer, history of cardiovascular disease; current major depressive episode/diagnosis or past history of panic disorder, psychoisis or bipolar disorder; history of alcohol or substance abuse other than cigarette smoking; allergy or sensitivity to bupropion; using psychoactive drug within last week; using medications which lower seizure threshold; used another investigational drug in past four weeks; using other smoking cessation treatments; using other tobacco products; have other household members participating in the study or another clinical study; have problem which would affect study compliance; presence of medically significant adverse effect related to the study treatment; inability to tolerate the study medication **Baseline characteristics** Not reported **Participant numbers and attrition** Total, n = 450 Bupropion, n = 226 Placebo n = 224. At 52 weeks 39% (89/226) had dropped out of the bupropion group and 48% (107/224) out of the placebo group	**Specific intervention** Bupropion hydrochloride SR (150 mg/day for first 3 days then 150 mg bid for 12weeks) **Comparator** Placebo	**Outcome 1** Sustained abstinence **% intervention group not smoking at 6 months:** 12% (27/226) **% comparator group not smoking at 6 months:** 2% (5/224) **Statistical test for comparison** P< 0.001 **Outcome 2** Point prevalence at week 26 21% for bupropion SR group and 10% for placebo group (p< 0.002)	12 month data not published and is not included in this report due to commercial confidentiality

Study Details	Participant details	Intervention Details	Results	Comments
Herzberg 2001[51] **Design of study** Double-blind, parallel group **Schedule of study visits** Baseline assessment, 12 weeks treatment, with visits and assessments at weeks 1, 2, 4 ,8 and 12 and follow-up at 6 months. At study vists participants were counselled and encouraged to remain abstinent (paid $100) **Outcome measures** Abstinence **Definition of smoking cessation** Continuous abstinence **Method** Daily smoking diary plus expired CO levels 10ppm or less at each study visit	**Inclusion/exclusion** Fifteen patients from a Veterans Medical Affairs Centre who expressed a desire to stop smoking. Patients were either receiving no psychotrophic medication or a stable psychotrophic regimen (same dosage and drug for at least 6 months before the study). All subjects met DSM-IV criteria for a primary diagnosis of post-traumatic stress disorder **Baseline characteristics** Mean age (years): 50 (range, 47 - 58) Pack-year history: mean, 57 (range, 21 - 203) Daily smoking rate: mean, 33 (range, 15 - 99) Heavy smoking (>25 cigarettes/day): 7/15 **Participant numbers and attrition** Total, n = 15 Bupropion SR = 10, Placebo = 5. 7/15 did not complete 12 weeks treatment: 6 pts started smoking again (2/10 on bupropion, 4/5 on placebo); 1 bupropion patient withdrew due to adverse effects	**Specific intervention** Bupropion SR (initially 150 mg for 3-4 days then increased to 150 mg b.i.d). **Comparator** Placebo	**Outcome** Sustained abstinence **% intervention group not smoking at 3 months:** (12 weeks) 60% **% intervention group not smoking at 6 months:** 40% **% comparator group not smoking at 3 months:** (12 weeks) 20% **% comparator group not smoking at 6 months:** Not stated **Odds Ratio for comparison** None reported	

Study Details	Participant details	Intervention Details	Results	Comments
Tashkin 2001 [45]/GSK 2000 [44] **Design of study** Double-blind, parallel group **Schedule of study visits** 4 , 7, and 12 weeks, and 6 months **Outcome measures** Primary outcome was continuous abstinence weeks 4-7. Secondary outcomes included continuous abstinence at weeks 4-12 and 4-26 and point prevalence at each clinic visit and at 6 month follow-up visit **Definition of smoking cessation** Continuous abstinence was defined as no smoking . Point prevalence of abstinence was defined as abstinence during previous 7 days **Method** Participant report of 0 cigarettes/day confirmed by exhaled carbon monoxide values of 10 parts per million (ppm) or less	**Inclusion/exclusion** Current smokers with stage I or II COPD; aged 35 years or older; smoked 15 cigarettes or more per day for the previous year; had not stopped smoking for more than 3 months in the previous year; motivated to stop smoking. Exclude: Participants who had any serious or unstable medical disorders that might affect lung function or for which bupropion SR was contraindicated and current diagnosis of major depression **Baseline characteristics** (Bupropion SR; placebo) Sex: 113/206 (55%) M; 113/205 (55%) M Mean (SD) age: 53.2 years (9.0); 54.5 years (9.5) Mean (SD) cigs/day: 28.7 (11.1); 27.6 (10.2) Mean (SD) pack-year history (years): 52.6 (25.8); 51.4 (23.8) Mean (SD) age when started: 16.5years (3.5); 17.3 years (4.1) Mean Fagerstrom score (SD): 7.1 (1.7); 7.0 (1.7) **Participant numbers and attrition** Total, n = 404 Bupropion SR, n = 204 Placebo, n=200. At 6mths: Bupropion SR n = 129 Placebo n = 149	**Specific intervention** Bupropion SR 150 mg/day for days 1-3 then 150 mg twice a day for days 4-84 **Comparator** Placebo	**Outcome 1** Sustained abstinence **% intervention group not smoking at 3 months:** (12 weeks)18% (36/204) **% intervention group not smoking at 6 months:** 16% (32/204) **% comparator group not smoking at 3 months:** (12 weeks) 10% (20/200) **% comparator group not smoking at 6 months:** 9% (18/200) **Odds Ratio for comparison** None reported Differences in abstinence rates at 12 weeks (3 months) and 26 weeks (6 months) were statistically significant (p=0.021 and p=0.040 respectively)	12 month data not published and is not included in this report due to commercial confidentiality

Study Details	Participant details	Intervention Details	Results	Comments
GSK 1999[43] * **Design of study** Double-blind, parallel group **Schedule of study visits** Baseline visit, treatment visits (up until week 7), follow-up visits at weeks 12, 24, 36, 52, 56 and months 15, 18 and 24. **Outcome measures** Included continuous abstinence, point abstinence, median time to relapse, craving and adverse events over the eight follow-up times. **Definition of smoking cessation** Continuous abstinence was defined as no cigarettes over the specified time period. Point abstinence was defined as not smoking over the previous 7 day period. **Method** Participant self-report confirmed by exhaled carbon monoxide levels of less than 10 parts per million (10ppm). Where the participants self-report did not match the exhaled carbon monoxide findings the participant was assumed to have relapsed.	To enter the RCT part of the study participants had to have completed an open 7-week treatment period on bupropion and to have achieved abstinence. **Inclusion/exclusion** **Baseline characteristics** **Participant number and attrition**	**Specific intervention** Bupropion SR 300 mg/day **Comparator** Placebo	**Outcome** Sustained abstinence	
* The data for this study was supplied by the manufacturer and has had to be removed from this publication for reasons of commercial confidentiality				

9.6.3 Systematic review for NRT

REVIEW DETAILS
Author
Silagy 2001[24]
Objective: To determine the effectiveness of the different forms of NRT in achieving abstinence from cigarettes. To determine effect of setting, dosage and form of NRT, and level of support. To determine if combining differentf NRTs increases effectiveness.
Inclusion Criteria
Study design: RCTs or quasi-RCTs of NRT versus placebo or no treatment or where different doses of NRT were combined.
Participants: Smokers of either gender, irrespective of setting nad or/initial level of nicotine dependency. Studies which randomised therpaists, rather than smokers, to offer NRT or a control were included providing that the speciifc aim of the stduy was to examine the effect of NRT on smoking cessation. Trials which randomised physisians or other therapists to receive an educational intervention, which included encouraging their patients to use NRT, were not included.
Intervention: Comparisons of NRT versus placebo or no NRT control. Trials of different doses of NRT were also included.
Outcome: The review was confined to the outcome smoking cessation with follow-up of at least 6 months. In each study the strictest available definition of abstinence was used. Wherever possible sustained cessation rate rather than point prevelence was used. In trials where participants were lost to follow-up they were regarded as being continual smokers. A second objective was to determine the effectiveness of NRT in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit.
Exclusion Criteria: Studies that did not report cessation rates were excluded as were those with follow-up shorter than 6 months
Quality Assessment: Studies were assessed according to the rigour of their randomisation and whether this was sufficient to adequately control selection bias. The specific criteria or scale used is not stated in the report.

RESULTS
Total studies: n = 108
Types of studies: 36 studies were true RCTs. 5 were quasi-RCTs. 67 were RCTs for which the details of randomisation was not fully reported.
Type of smoker: Unclear
M/F ratio: Not stated
Level of nicotine dependence: Any
Fagerstrom score: Whole range 0 - 11. Smokers with score less than 7 were classed as 'low' dependency, those with 7 ot more, were classed as 'high' dependency.
Specific intervention: Nicotine chewing gum (2 mg or 4 mg or both or variable) for 3 weeks to 12 months; Nicotine transdermal patches 16 or 24 hour patches (doses not specified, but some studies compared patches of different strengths) for a minimum of 6 weeks to 3 months, with a tapering period in some trials; nicotine nasal spray (details not given in SR); nicotine inhalers/inhalators (details not given in SR); and nicotine tablets (details not given in SR. Comparisons of NRT versus placebo or no NRT control. Trials of different doses of NRT were also included.

In some analyses the level of support given was specified. Routine care was classed as low-intensity support. If the duration of time spent with the smoker exceeded 30 minutes at initial consultation or the number of further assessments or visits exceeded two, this was high-intensity support.

Comparator: Placebo; no treatment; bupropion (dosage details not given); for trials of combination therapies, patch, spray or gum alone (details not given).

Specific outcome: Effect on smoking cessation taken as percentage of participants abstinent (achieved cessation) at follow-up.

Definition of smoking cessation used: Definitions of abstinence varied considerably with 27 of the trials reporting the primary long-term outcome abstinence measure as a point prevelance, 75 as a sustained measure, and five making no specific mention in the report as to which approach was used. The one remaining study looked at a reduction in smoking rather than abstinence. All but 11 of the trials used some form of validation of self-reported smoking cessation. Validation of the abstinence was carried out by blinded methods (measurements of metabolites in body fluids) in 21 trials. Measurement of carbon monoxide in expired air was the most common form of validation used. However, the 'cut-off' level of carbon monoxide used to define abstinence varied from less than 4 to 11 parts per million. In one trial perticipants who smoked up to three cigarettes per week were still classified as abstinent (Abelin (1989).

Duration of follow-up: With the exception of 12 gum trials and 13 patch trials, participants were followed for at least 12 months.

Settings: Twenty-two studies were conducted in primary care. Five were in workplaces settings, two in a university clinic and one in a VA Medical Centre. Eight studies were in specialised smoking-cessation clinics and seven trials were in hospitals (i.e. patients usually with smoking-related illness). Three studies were of OTC NRT. The remaining trials were in participants from the community, most of whom had been recruited in response to media advertisments, but who were treated in clinics.

Participants: All trials included both male and female participants except for two: Kornitzer 1987 included only males and Pirie 1992 included only females. The range of the mean number of cigarettes smoked (per day) by particiapnts in those studies included in the review which provided this data was 15.5 to 32.9.

One study included only relapsed smokers (Gourlay 1995).

Quality of included studies: Thirty-six studies reported randomisation procedures in sufficient detail to be rated A for their attempts to control selection bias. The majority of studies were rated B because they had either did not report how randomisation was performed or reported it in insufficient detail to determine whether a satisfactory attempt to control selection bias had been made. A small number of trials randomised to treatment according to day of week or clinic attendance (Page 1986, Richmond 1990, Russell 1983), birthdate (Fagerstrom 1984), or smokers' clinic group (Mcgovern 1992).

COMMENTS

Combination therapy not main focus of review.

With the exception of 12 gum trials and 13 patch trials, participants were followed for at least 12 months.

9.6.4 Systematic review of Bupropion

REVIEW DETAILS
Author
Hughes 2000[40]
Objective: To assess the effectiveness of antidepressant medications in aiding long-term smoking cessation. Bupropion is one of the drugs included in this SR
Inclusion Criteria
Study design: Randomized controlled trials. The control was placebo or an alternative therapeutic intervention
Participants: Any smokers
Intervention: Treatment with any drug with antidepressant properties.
Outcome: The outcome measure was abstinence from smoking assessed at follow-up at least 6 months from the start of treatment. In each study the strictest available criteria to define cessation were used, so figures for sustained abstinence were extracted in preference to point prevalence where both were presented. In studies that used biochemical validation of cessation, only those subjects meeting those criteria were counted as having stopped smoking. Those lost to follow-up were counted as continuing to smoke.
Exclusion Criteria: Trials with less than six months follow-up were excluded from the review.
Quality Assessment: According to method of randomisation, definition of abstinence and whether biochemical validation was used. Classification A to D(A appropriate method of randomisation with proprer concealment of allocation; B no details of randomisation methodology; C quasi-randomisation open to potential allocation bias; D no information) .

RESULTS
Total studies: n = 5
Types of studies: RCTs (5)
Type of smoker: Unclear
M/F ratio: Not stated for review overall
Level of nicotine dependence: Not Stated
Fagerstrom score: Not stated. See comments box for more information on level of nicotine dependence
Specific intervention: Bupropion standard release and sustained release, 100 to 300 mg per day. The duration of treatment ranged from 7 weeks to 45 weeks
Comparator: Placebo, different doses of bupropion and nicotine patch (24 h, 21 mg).
Specific outcome: Smoking abstinence
Definition of smoking cessation used: Continuous abstinence at 12 months in all studies except one of 42 patients (Ferry 1992) which reported abstinence (definition not stated) at 6 months and another that reported continuous abstinence at 2 years (one year after the end of treatment) (Hays 2000). Two of the studes that reported continued abstinence at 12 months defined this as continuous abstinence from day 22 or day 29 to 12 months (Hurt 1997 and Ferry 1994 respectively).

Duration of follow-up: 6-24 months

Settings: Two of the studies (Hurt 1997 and Jorenby 1999 (615 and 893 participants respectively) recruited patients via advertisements. The study by Hays (2000) (n=429) recruited 784 community volunteers. Details of setting for the other two studies (combined n=232) are not stated in SR.

Participants: In the three large studies included in the SR the proportion of female patients was 51% (of 429), 55% (of 615), 52% (of 893). The average ages of the patients were 46, 44 and 43 years respectively. The 42 participants in the study by Ferry (1992) were all male. No information is given regarding the 190 participants in the Ferry (1992) study.

Quality of included studies: The studies included in the SR are listed below with their quality rating: Ferry 1992 (B); Ferry 1994 (B); Hurt 1997 (B); Jorenby 1999 (B); Hays 2000 (B).

COMMENTS

Although this SR included all antidepressant medication used for smoking cessation, no pooling of results for antidepressants as a whole was performed and studies for each type of anti-depressant were analysed separately. Therefore, only information pertaining to bupropion are extracted and all the information on this form pertains specifically to the bupropion studies only, e.g the number of studies is the number of bupropion studies not the total number in the review.

The three largest of the five studies included 1937 of the 2169 participants included in the SR. In these three studies the average number of cigarettes smoked per day ranged from 25 to 46.

9.7 ADVERSE EVENT DATA EXTRACTION TABLES

9.7.1 Adverse Event Data Extraction Tables - NRT

9.7.1.1 NRT Adverse events reported in RCTs

9.7.1.1.1 Cardiovascular events (healthy subjects)
9.7.1.1.2 Cardiovascular events (participants with heart conditions)
9.7.1.1.3 Pregnancy
9.7.1.1.4 Diabetes mellitus
9.7.1.1.5 Abuse Potential
9.7.1.1.6 Cutaneous reactions
9.7.1.1.7 Body weight
9.7.1.1.8 Endothelial function

9.7.1.2 Adverse events reported in non-randomised controlled studies

9.7.1.2.1 Cardiovascular

9.7.1.3 Adverse events reported in uncontrolled studies

9.7.1.3.1 Incidence
9.7.1.3.2 Cardiovascular events (healthy subjects)
9.7.1.3.3 Cardiovascular events (participants with heart conditions)
9.7.1.3.4 Pregnancy
9.7.1.3.5 Cutaneous reaction
9.7.1.3.6 Oral Mucosa
9.7.1.3.7 Blood lipid levels
9.7.1.3.8 Abuse potential

9.7.1.4 Adverse events reported in case-control studies
9.7.1.4.1 Incidence

9.7.1.5 Adverse events reported in surveillance studies

9.7.1.6 Adverse events reported in systematic reviews

9.7.1.1 NRT Adverse events reported in RCTs

9.7.1.1.1 NRT Adverse events reported in RCTs - Cardiovascular events (healthy subjects)

Study details	Participant details	Results	Comments

Author, Year Fishbein 2000 [54] **Study design** RCT **Intervention details** **Specific intervention** Nicotol NS (3 mg administered as 3 sprays of 0.5 mg per nostril) **Comparator** Placebo **Duration of therapy** Not stated, measurements at only one time point **Duration of follow-up** 115 minutes post-administration	**Number of participants** Intervention: n = 10 Comparator: n = 10 **Inclusion/exclusion** Male and female first-year medical students aged 21 to 29 years. Participants had to have abstained from all nicotine-containing products for at least 1mth before the study; Exclude: Pregnancy and breast feeding, allergy to nicotine, use of medicine or caffeine within 12hrs before study, presence of hypertension, diabetes or other chronic diseases **Baseline characteristics** Mean (SD) age: 23.7 (2.2) years (nicotine); 22.8(1.1) years (placebo) **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**Intervention** **List of adverse events** Looks at biochemical and clinical effects over a short period. Peak change from baseline SBP 7.13% (SD 9.42) (p=0.03 compared with placebo) Mean peak SBP 5 mins after NRT administration 135.4 (SD 12.30) mmHg No statistically significant difference in DBP or HR compared with placebo (p=0.8 and p=0.07 respectively) Adverse events Using a scale of 1 (no pain) to 5 (severe pain): general irritation 8/10 (80%) Nose/throat burning 7/10 (70%) **Comments** N/A **Comparator** **List of adverse events** Looks at biochemical and clinical effects over a short period. Peak change from baseline SBP -1.61 (SD 7.26)% **Comments** N/A	Participants were randomised in a double-blind manner, blocking on gender. However, 14/20 participants correctly identified their intervention assignment

Study details	Participant details	Results	Comments
Author, Year Allen 1995 [58] **Study design** RCT **Specific intervention** 2 mg nicotine gum **Comparator** Placebo **Duration of therapy** 8 weeks **Duration of follow-up** Tests conducted at baseline, 4wks and 8 wks	**Number of participants** Intervention: n = 22 were abstainers who used the 2 mg gum Comparator: n = 34 abstainers who were given placebo **Inclusion/exclusion** Users of smokeless tobacco. Study focused on those who abstained from tobacco use **Baseline characteristics** Mean (SD) age: 34.1 (10.3) Sex: 100% M **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**Intervention** **List of adverse events** Adverse events not reported . See comments section for data collected **Clinical significance** NA **Comments** 2 mg nicotine gum group No change in the mean values for SBP, DBP, HR, Total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides were seen from baseline to either time point in the study **Comparator** **List of adverse events** NA **Comments** No change in the mean values for SBP, DBP, HR, Total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides were seen from baseline to either time point in the study, with either nicotine gum or in the placebo group	**Comments** It should be noted that these baseline mean values were not outside the normal range The paper specifies that those patients with clinical hypertension were excluded and those with mild hypertension (DBP >90, <100mmHg) at baseline did not have reduced BP at 8 wks

Study details	Participant details	Results	Comments
Author, Year Khoury 1996 [62] **Study design** RCT **Specific intervention** Transdermal nicotine patches (14 mg/day for Fagestrom score of 5 or 6, 21 mg/day for Fagestrom scores of 7 or more) **Comparator** Placebo containing 13% of nicotine of treatment **Duration of therapy** 2 wks **Duration of follow-up** Concurrent with duration of study	**Number of participants** Intervention: n = 25 Comparator: n = 25 **Inclusion/exclusion** Study population of healthy smokers, motivated to quit. All participants received psychological support. Evidence of dependence on smoking as indicated by Fagestrom score of 5 or more. Exclude: History of hypersensitivity to cutaneous adhesives, peptic ulcer, diabetes mellitus, renal impairment (creatinine >28 upper limit of normal), advanced pulmonary disease or stroke; known heart disease, such as history of MI, angina pectoris, valvular disease or positive exercise test; subjects exhibiting resting heart rate > 110 bpm, abnormal ECg at rest, diastolic BP > 95 mm Hg, systolic BP > 180 mm Hg, episodes ofST-segment depression or presence of complex ventricular arrhythmias during the screening Holter monitoring **Participant characteristics** Mean age: 42.5 years treatment, 40.6 years placebo Sex: 13/25 M treatment, 13/25 M placebo Mean no. of smoking years: 24.3 treatment, 22.4 placebo Fagestrom score 5-6: 9 treatment, 7 placebo Fagestrom score 7-11: 13 treatment, 15 placebo Mean CO reading at baseline: 14.2 ppm treatment, 13.2 ppm placebo Mean urine cotinine: 8.8 micromol/l treatment, 8.1 micromol/l placebo **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** Minor rhythm disturbances, 1 No significant differences in ECg parameters, heart rate or BP between treatment and placebo groups: Treatment group heart rate (bpm) screening = 76.8, day 0 = 74.0, day 14 = 71.3 compared with placebo group 74.5, 73.2 and 69.6. Treatment group systolic BP (mm Hg) screening = 108.7, day 0 = 108.9, day 14 = 106.5 compared with placebo group 111.3, 110.6 and 105.3. Treatment group diastolic BP (mm Hg) screening = 74.0, day 0 = 69.7, day 14 = 68.2 compared with placebo group 73.2, 71.4 and 70.5 No significant adverse cardiovascular effects observed for transdermal nicotine patches **Comments** **Comparator** **List of adverse events** Minor rhythm disturbances, 3 **Comments**	RCT to examine cardiovascular effects and safety of transdermal nicotine patches. Effectiveness of smoking cessation also reported

Study details	Participant details	Results	Comments
Author, Year Lucini 1998 [55] **Study design** RCT (crossover) **Specific intervention** 21 mg/24/h nicotine patch (Nicotell TTS 30). **Comparator** Placebo; standardised smoking day (n=7 cigarettes) **Duration of therapy** 3 days **Duration of follow-up** As therapy	**Number of participants** Intervention: n = 27 Comparator: Not stated **Inclusion/exclusion** 27 volunteers from a smoking cessation program **Baseline characteristics** Mean (SD) age, 43 (2) years Mean (SD) Fagestrom scale score: 8.2 (0.2) Mean (SD) no. of years smoking: 22 (2) **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**Intervention** **List of adverse events** At rest, arterial pressure levels and variablity were similar in all three examined conditions (standardised smoking day, nicotine patch and placebo). The RR interval appeared significantly reduced, in both the smoking and nicotine patch groups compared to placebo, and RR variability appeared reduced by smoking and to a lesser extent nicotine patch When standing, RR interval and variability differences were not significant between groups, and no differences were observed between groups in arterial pressure **Comments** Useful information on autonomic effects of nicotine patch Authors state: Active nicotine-patch treatment leads to an autonomic state intermediate between that observed during smoking or placebo patch administration, indicating that nicotine patch treatment produces only minor disturbances of autonomic cardiac control **Comparator** **List of adverse events** See above **Comments**	

Study details	Participant details	Results	Comments
Author, Year Sahba 2000 [59] **Study design** RCT (crossover) **Specific intervention** Nicotine patch 21 mg **Comparator** Placebo **Duration of therapy** Single dose study **Duration of follow-up** One day	**Number of participants** Intervention: n = 21 Comparator: n = 21 **Inclusion/exclusion** Non-smokers or mild to moderate smokers: **Participant characteristics** Sex: 12/21 M Mean (SD) age: (non-smokers) 35.4 (4.2), (smokers) 38.3 (7.1) Years of tobacco use in smokers mean (SD): 12.4 (5.2) Mean (SD) no. cigarettes/day: 12.2 (5.1) Mean (SD) Fagerstrom score 3.5 (1.2) Expired CO (ppm) non-smokers 3 (SD 2), smokers 9 (SD 4) **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** % of maximum response (non-smokers; smoker) : Response to bradykinin: 54.3 (SD14.9); 48.3 (SD 13.7) Response to nitroprusside: 96 (SD 25), 106 (SD 42) Changes in mean arterial BP (MABP) and heart rate (HR): 1. After one hour in nonsmokers from 87 (SD 4) to 111 (SD 5) mmHg; 2. After 2 hours on smokers from 83 (SFD 2) to 98 (SD 6) mm Hg. Heart rate only changed in nonsmokers from 69 (SD 2) to 83 (SD 3) at one hour. The increase in MABP and HR was accompanied by nausea, lightheadedness, mild headache, and seating in non-smokers Thromboxane b2 increased in non-smokers after 1 hour use of patch **Clinical significance** **Comments** The main finding of this investigation was that transdermal nicotine administration to non-smokers blunted the vasodilator response to bradykinin compared with that in smokers, suggesting a pivotal role for nicotine in endothelial dysfunction in cigarette smokers **Comparator** **List of adverse events** % of maximum response (non-smokers; smoker) Response to bradykinin 88.1 (SD 17.9); 56.0 (SD 16.6) Response to nitroprusside 107 (SD 23), 96 (SD 25) There were no changes in MABP or HR in the placebo group **Comments**	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Krivokapich 1984 [63] **Study design** RCT (crossover)	**Number of participants** Intervention: n = 6 Comparator: n = 6 **Inclusion/exclusion** Six paid volunteers with 'normal' resting BP and 12-lead ECg at time of recruitment **Baseline characteristics** Sex: 100% M Mean (SD) age: 27.3 (2.6) Mean (SD) cigarettes smoked per day: 26 (5) Mean (SD) years smoked: 8.8 (5.1) years **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**List of adverse events** Limited details reported. gum has no effect on CO. gum has no significant acute effect on heart rate. gum has no effect on BP. gum had any acute effect on ECG. **Comments** No acute cardiovascular effects reported for nicotine gum	
Intervention details		Results – comparator	
Specific intervention High (4 mg) and low (2 mg) nicotine gum, (Nicorette) **Comparator** High (2 mg) and low (0.2 mg) nicotine cigarettes **Duration of therapy** 2 hours for each intervention or comparator **Duration of follow-up** NA (acute response study) Note: All participants abstained from cigarettes for a minimum of 11 hrs prior to study. Treatments and comparators gven randomly on consecutive days		**List of adverse events** CO at 10 and 90 mins from baseline: Significant rise in CO ($p = 0.02$) at 10 mins with cigarettes compared with gum, irrespective of dose Increase in heart rate over baseline: Only 2 mg cigarettes have significant effect ($p < 0.001$). Significant dose effect ($p = 0.01$), higher doses of nicotine have more effect regardless of method of delivery ECG: no changes Blood pressure: Systolic and diastolic BP increased in a dose dependent manner at 5 mins after cigarettes. gum had no effect. Cigarettes increase CO acutely. Only the high nicotine cigarettes (2 mg) effect heart rate acutely. Cigarettes increase BP acutely in a nicotine dose dependent manner. Cigarettes had no acute effect on ECG **Comments** NA	

Intervention details		**Results – Comparator**	
Specific intervention Nicotine patch (PROSTEP 22 mg/day, 24 h) **Comparator** Two cigarettes, or 48hrs no smoking **Duration of therapy** 34 hrs **Duration of follow-up** Duration of testing		**List of adverse events** Relative blood flow when smoking was significantly decreased compared with non-smoking control Average heart rate, BP, fibrinogen, haemoglobin, haematocrit, white blood cell count, platelet count, carboxyhaemoglobin, vasopressin and norepinephrine were all significantly higher for smoking compared with. Non-smoking control **Clinical significance** **Comments**	

9.7.1.1.2 NRT Adverse events reported in RCTs - Cardiovascular events (participants with heart conditions)

Study details	Participant details	Results	Comments
Author, Year Joseph 1996 [53] **Study design** RCT **Specific intervention** Transdermal nicotine (Nicoderm) 21 mg/day for 6 wks, 14 mg/day for 2 wks and 7 mg/day for 2 wks **Comparator** Placebo patch of same appearance and odour **Duration of therapy** 10 wks **Duration of follow-up** 14 wks (adverse event), 24 wks (efficacy)	**Number of participants** Intervention: n = 294 Comparator: n = 290 **Inclusion/exclusion** Minimum age 45 years; smoking minimum 15 cigarettes/day; must have smoked for at least 5 years, made a minimum of 2 previous attempts to quit and had an expired CO level of > 8 ppm; one or more of the following diagnosed conditions: a history of MI, a history of coronary-artery bypass surgrey or angioplasty, stenosis of at least 50% in at least one major coronary arteryas seen with coronary angiography, or a clinical history of angina, congestive heart failure, cor pulmonale, arrhythmia, peripheral vascular disease or cerebrovascular disease Exclude: Suffering from MI, unstable angina, CABg, angioplasty or hospitalisation for cardiac arrhythmia in the two weeks befor ethe study **Baseline characteristics** (Treatment group; Placebo) Mean age: 61 years; 60 years Mean no. cigarettes/day: 28; 28 Mean duration of smoking: 44 years; 44 years 2-5 Previous attempts to quit: 184; 181 More than 5 previous attempts to quit: 110; 109 Nicotine content of usual brand of cigarettes 0.9 mg or less: 140; 145 Mean Fagerstrom score: 6.4; 6.4 Mean expired CO: 25 ppm; 25 ppm **Proportion of participants reporting an adverse event** Intervention:47 (16.2%) Comparator: 47 (16.2%)	**Intervention** **List of adverse events** Primary end points: Death, 1; MI, 0; Cardiac arrest, 1; Admission for increased severity of angina, 7; Admission for arhythmia, 5; Admission for congestive heart failure, 2 Total, 16 (5.4%) Secondary end points: Admission for peripheral vascular disease, 3; Admission for cerebrovascular disease, 4; Admission for other reasons, 16; outpatient visit for increased severity of atherosclerotic cardiovascular disease, 12; Total, 35 (11.9%); All end points, 48 (16.3%) No. known to be smoking (at least one cigarette in preceding 3 days) at time of adverse event Primary end points: Death, 1; MI, 0; Cardiac arrest, 0; Admission for increased severity of angina, 4; Admission for arrhythmia, 4; Admission for congestive heart failure, 0 Total, 9 Secondary end points: Admission for peripheral vascular disease, 1; Admission for cerebrovascular disease, 3; Admission for other reasons, 6; Outpatient visit for increased severity of atherosclerotic cardiovascular disease, 7; Total, 17; All end points, 26 Not significantly different from control group. **Comments** N/A **Comparator** **List of adverse events** Primary end points: Death, 6; MI, 1; Cardiac arrest, 1; Admission for increased severity of angina, 10; Admission for arhythmia, 3; Admission for congestive heart failure, 2; Total, 23 Secondary end points: Admission for peripheral vascular disease, 5; Admission for cerebrovascular disease, 3; Admission for other reasons, 13; outpatient visit for increased severity of atherosclerotic cardiovascular disease, 7; Total, 28; All end points, 47 No. known to be smoking (at least one cigarette in preceding 3 days) at time of adverse event: Primary end points: Death, 3; MI, 1; Cardiac arrest, 0; Admission for increased severity of angina, 5; Admission for arhythmia, 3; Admission for congestive heart failure, 1; Total, 13 Secondary end points: Admission for peripheral vascular disease, 3; Admission for cerebrovascular disease, 2; Admission for other reasons, 9; Outpatient visit for increased severity of atherosclerotic cardiovascular disease, 5; Total, 19; All end points, 32 **Clinical significance** N/A **Comments** N/A	Patients in the treatment group gained an average of 1.4 kg between baseline and wk 14 compared with 0.3 kg in control group (p = 0.001). No significant differences in BP or pulse

Study details	Participant details	Results	Comments
Author, Year Keely 1996 [60] **Study design** RCT **Specific intervention** In sequence: cigarette (1 mg nicotine), 50 m L nicotine nasal spray (0.5 mg), 2nd cigarette **Comparator** As intervention, with placebo spray substituted **Duration of therapy** NA, study of acute effects **Duration of follow-up** Concomitant with study Note: All patients were asked to refrain from smoking for at least 12 hrs and all vasoactive medications (including beta-blockers, calcium-channel blockers, long-acting nitrates and diphenhydramine) were discontinued for at least 5 half-lives before the study. Patients were studied after overnight fast and received 5 mg oral diazepam prior to procedure	**Number of participants** Intervention: n = 14 Comparator: n = 5 **Inclusion/exclusion** Consecutive patients referred for cardiac catheterization to evaluate chest pain who had smoked 10 or more cigarettes per day for 10 or more years. Patients excluded for >50% luminal narrowing of the left main coronary artery. Initially 21 patients; study aborted in 2 due to chest pain and ECg changes after first cigarette **Participant characteristics** Age: 35 -60 years Sex: 12/19 M **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** See below **Comments** N/A **Comparator** **List of adverse events** For the 45 non-diseased coronary arterial segments analysed (34 treatment group and 11 placebo) there was a 5% (SD 2%) reduction in minimal luminal diameter (p = 0.009) compared with baseline after smoking first cigarette. The 9 focally stenosed segments showed no significant reduction. Neither administration of nicotine spray or smoking of second cigarette caused significant change in minimal luminal diameter of either non-diseased or stenosed vessels Heart rate and systolic arterial pressure and consequently rate-pressure product (estimate of myocardial oxygen demand) did not increase significantly except after smoking first cigarette: Heart rate, baseline = 72 +/- 3 bpm, first smoke = 80 =/- 3 bpm (p<0.001). Systolic arterial pressure, baseline = 136 +/- 6, first smoke = 142 +/- 7 (p=0.0112) **Comments** Cigarette smoking causes an acute increase in myocardial oxygen demand and concominant coronary artery vasoconstriction. Subsequent increases in serum nicotine concentration (regardless of the method of delivery) have no further effects on these parameters. This may have consequences for decisions about nicotine replacement therapy in patients who do not reliably discontinue smoking whilst on treatment	

Study details	Participant details	Results	Comments
Author, Year Tzivoni 1996 [64] **Study design** RCT Participants had 48 hours of ambulatory ECg monitoring immediately before the study, for the first 48 hours of patch application and after two weeks **Specific intervention** Nicotine patches **Comparator** Placebo patches **Duration of therapy** 2 weeks **Duration of follow-up** 2 weeks	**Number of participants** Intervention: n = 52 Comparator: n = 54 **Inclusion/exclusion** Participants with CAD taking part in a smoking cessation program **Baseline characteristics** Not reported **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** No change in resting HR, SBP, DBP, between screening and the two phases of the study. Number of iscaemic episodes at screening 2.5, after patch appliction 3.8, and after 2 weeks 2.9 (NS trend). Duration of ischaemia was 22, 25.7 and 21.4 minutes respectively (NS) **Comments** N/A **Comparator** **List of adverse events** No change in resting HR, SBP, DBP, between screening and the two phases of the study.Number of iscaemic episodes at scrreening 3.5, after patch appliction 5.0, and after 2 weeks 5.4 (NS trend). Duration of ischaemia not stated **Comments** N/A	Conference abstracts - only limited information

Study details	Participant details	Results	Comments
Author, Year Tzivoni 1998 [115] **Study design** RCT **Specific intervention** 14 or 21 mg per 24h mg or 21 (smokers of 20 or more per day) mg/24 hrs nicotine patches (Nicotinell) **Comparator** Placebo patches 2 and 3 mg nicotine per 24 hours **Duration of therapy** 2 weeks **Duration of follow-up** 2 weeks	**Number of participants** Intervention: n = 52 Comparator: n = 54 **Inclusion/exclusion** Presence of CAD, based on angiography (> 70% narrowing of at least one major coronary artery), stable angina pectoris with positive exercise test, documented previous MI; Nicotine dependent, smoking at least 15 cigarettes per day for 5 or more years, with a Fagerstrom score of 5 or more Exclude: Hypersensitivity to any adhesive cutaneous application; MI, coronary bypas surgery, coronary angioplasty or stroke within 3 mths of screening; >12 ischaemic episodes during 48hr ECg; BP diastolic > 110 mm Hg or systolic > 200 mm Hg; Reduced left ventricular function; Clinical signs of congestive heart failure **Baseline characteristics** Bupropion group: Sex: 48/52 M Mean age: 54.5 years Mean smoking duration: 36 years Mean no. cigarettes per day: 25 Mean Fagerstrom score: 7.7 Mean no. of previous attempts to stop smoking: 2.1 Mean nicotine content per cigarette: 0.9 Placebo group: Sex: 48/54 M Mean age: 53.1 years Mean smoking duration: 35 years Mean no. cigarettes per day: 28 Mean Fagerstrom score: 7.8 Mean no. of previous attempts to stop smoking: 1.6 Mean nicotine content per cigarette: 0.9 **Proportion of participants reporting an adverse event** Intervention: 1 (1.9%) Comparator: 1 (1.9%)	**Intervention** **List of adverse events** One patient complained of angina at rest and 1 patient developed unstable angina with doccumented ischaemia. Heart rate, BP, ambulatory ECg and exercise testing showed no significant differences between treatment and control groups during the study **Comments** N/A **Comparator** **List of adverse events** One patient who had worsening angina underwent cardiac catheterisation and coronary artey bypass surgery **Comments** N/A	Efficacy: treatment group, 14 (52%) claimed abstinence at 2 wks. Control group 7 (13%) claimed abstinence at 2 wks Authors conclude that this study demonstrated that nicotine patches can be applied to coronary patients trying to quit smoking without exposing them to increased cardiovascular risk

Study details	Participant details	Results	Comments
Author, Year Working Group for the study of Transdermal Nicotine in patients with CAD 1994 [57] **Study design** RCT **Specific intervention** nicotine patch 14 mg to 21 mg /day **Comparator** Placebo **Duration of therapy** 5 weeks Duration of follow-up **5 weeks**	**Number of participants** Intervention: 77 Comparator: 79 **Inclusion/exclusion** Smokers with stable coronary artery disease (CAD) **Participant characteristics** Mean (SD) age: Patch group, 56.0 (7.5); placebo group, 55.9 (8.1) Sex: 124/156 M Mean number of cigarettes smoked: 33 Mean years smoked: 38 years Mean Fagerstrom score: 8 Average number of previous quit attempts: 6 **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** 3/77 participants withdrew due to adverse events. The number of angina attacks fell from 10/week to 5/week at week 5. Ambulatory ECg monitoring did not reveal any statistically significant change from baseline at any study week. No increases on nocturnal arrhythmia or ischaemic St segment episodes were noted Heart rate was not altered Mean body weight increased by 2.2kg (greater than placebo $p<0.05$). Weight gain was greater in those who stopped smoking : mean 3.3kg ($p<0.05$ compared with Placebo) Adverse events were reported by 50% of patients in each tretament group , however, only transient itching at the patch application site was reported more often on active than placebo 36% vs. 9% Mean changes in blood chemistry and haematology variables were generally not significantly different between active and placebo tretaments **Comments** N/A **Comparator** **List of adverse events** 8/79 withdrew due to adverse events The number of angina attacks fell from 16/week to 7/week at week 5 Ambulatory ECg monitoring did not reveal any statistically significant change from baseline at any study week. No increases on nocturnal arrhythmia or ischaemic St segment episodes were noted Heart rate was not altered Mean body weight increased by 1.3kg and was greater in those who stopped smoking : mean 3.3kg Adverse events reported more ofetn on placebo than on active were dizziness, insomnia, diarrhoea, body aches, nervousness and angina **Comments** N/A	Short term use of nicotine patch: only five weeks.

9.7.1.1.3 NRT Adverse events reported in RCTs - Pregnancy

Study details	Participant details	Results	Comments
Author, Year Hardardottir 1998[118] (main publication of this study is Onken 1997[69] **Study design** RCT (crossover) **Specific intervention** Nicotine patch 21 mg **Comparator** Smoking ad libitum **Duration of therapy** 7 days **Duration of follow-up** 7 days	**Number of participants** Intervention: 13 Comparator: unclear **Inclusion/exclusion** Pregnant females, aged 18 years or older, 24 to 36 weeks gestation, who smoked at least 15 cigarettes per day **Baseline characteristics** Not reported **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**Intervention** **List of adverse events** Maternal SBP, DBP and MABP increased significantly during patch days compared with baseline and with smoking days (p< 0.01) n=7). The maternal heart rate, FHR. UA, UMB, and MCA RI did not differ between smoking and patch days. Serum nicotine levels did not differ between the groups (p=0.08, n=5) **Clinical significance** Higher maternal BP with patch compared with smoking with comparable nicotine blood levels may suggest some adverse effect of patch. No difference in foetal cardivascular effects **Comments** N/A **Comparator** **List of adverse events** See above **Comments** N/A	Same study as full manuscript Oncken 1997 [69]

Study details	Participant details	Results	Comments
Author, Year Oncken 1997 [69] (also published as Hardottir 1996[118]) **Study design** RCT (crossover) **Intervention details** **Specific intervention** 21 mg nicotine patch **Comparator** Smoking ad libitum **Duration of therapy** 8 hrs **Duration of follow-up** Concurrent with study	**Number of participants** Intervention: n = 15 Comparator: n = 15 **Inclusion/exclusion** At least 18 years; gestation, 24-36 wks; self-reported smoking of 15 cigarettes/day for preceding year Exclude: Foetal growth restriction (estimated foetal wgt < 10th centile for gestational age); hypertension (BP 14/90 mm Hg or greater); alcohol or illegal drug use during this pregnancy; positive urine toxicology screen; use of other tobacco products; salivary cotinine 85 ng/ml or less; Foetal anomalies; foetal arrhythmia; placenta previa **baseline characteristics** Mean (SD) age: 28 (5.4) years Mean (SD) cigarettes/day, 20.2 (5.2) Mean (SD) nicotine/cigarette, 1.0 (0.2) mg Mean (SD) plasma cotinine: 127 (45) ng/ml Mean (SD) gestational age: 28 week 3 days (20 days) **Proportion of participants reporting an adverse event** Intervention:NA Comparator: NA	**Intervention** **List of adverse events** Haemodynamic measurements were obtained before and after the onset of smoking or patch placement The plasma AUC for nicotine during patch use was 93 ng-hour/ml (p=0.77 compared to whilst smoking) The mean change in the middle cerebral artery RI from baselien to 4 hours later was -0.0002 (SD 0.008) (9=0.3 compared to whilst smoking) No clinically significant adverse event or pregnancy complications during study Significant time effects for systolic BP (p<0.001) and maternal heart rate (p<0.001) occuring 2 hrs after baseline measurements. Diastolic BP changed significantly over time (p=0.007) and the condition x time interaction was significant (p=0.004) **Comments** Changes in the middle cerebral resistance index (RI) are an indirect measure of foetal hypoxia Acute effects of nicotine on measures of foetal wellbeing are apparently similar regardless of method of delivery **Comparator** **List of adverse events** The plasma AUC for nicotine during patch use was 89 ng-hour/ml (p=0.77 compared to whilst using patch) The mean change in the middle cerebral artery RI from baseline to 4 hours later was -0.02 (SD 0.015) (9=0.3 compared to using patch) **Comments** N/A	The study had greater than 80% power to detect a 25% difference an a change of 2 SDs in the middle cerebral artery RI between treatments Study primarily designed to compare acute effects of smoking and nicotine patch; short term use only, no follow-up monitoring of adverse event

Study details	Participant details	Results	Comments
Author, Year Wisborg 2000 [29] **Study design** RCT **Intervention details** **Specific intervention** Nicotine patch (16 hour) 15 mg (8wks), 10 mg (3wks) **Comparator** Placebo **Duration of therapy** 11 weeks **Duration of follow-up** During pregnacy and up to 12 mths postpartum	**Number of participants** n = 124 **Inclusion/exclusion** Healthy pregnant women who smoked 10 or more cigarettes per day and were less than 22 weeks pregnant **Baseline characteristics** Mean age: 28 years Mean (SD) consumption of cigarettes per day 13.4 (nicotine group) and 14.2 (4.4) placebo group. Mean salivary cotinine: approx. 230. Information on number of previous attempts at quitting unclear **Proportion of participants reporting an adverse event** NA	**List of adverse events** 11 women did not use the patches due to adverse events. Adverse events included skin reaction, headache, palpitations, nausea. (few details given) Mean birth weight was 3457g in nicotine group and 3271g in the placebo group (mean difference 186g (95% CI 35 to 336) Proportion of infants with weight under 2500g was 3% and 9% in the nicotine and placebo groups respectively (RR 0.4, 95% CI 0.1 to 1.1). Adjustment for preterm delivery, smoking habits, and other factors yielded similar results Among children born after 37 weeks' gestation mean birth weights were 3539g and 3381g respectively (mean diff 157g 95% CI 25, 291g) The rate of pre-term delivery was 8% in the nicoitne group and 10% in the placebo group (RR 0.8 95% CI 0.4, 1.7) **Comments** Use of nicotine patches was low with only 17% using all the 15 mg patches and 1% using all the 10 mg patches. Thus data cannot reliably inform about safety or otherwise of nicotine patches in pregnancy	

9.7.1.1.4 NRT Adverse events reported in RCTs - Diabetes mellitus

Study details	Participant details	Results	Comments
Author, Year Epifano 1992 [61] **Study design** RCT (crossover) **Specific intervention** Nicotine patch (30cm2) **Comparator** Placebo; Smoking **Duration of therapy** 2 days **Duration of follow-up** After 12 hours	**Number of participants** Intervention: n = 12 Comparator: n = 12 in each group **Inclusion/exclusion** Patients with Fagerstrom score 6 and Type 2 diabetes mellitus **Baseline characteristics** Mean (SEM) age: 52 (2) years **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** Results of parameters related to glucose tolerance given: after nicotine patch; after placebo; or after smoking Baseline plasma glucose: 8.5 (SEM 0.29) mmol/l; 8.7 (SEM 0.33) mmol/l 8.6 (SEM 0.26) mmol/l (NS diffs No difference between any treatment for effect on plasma C-peptide at baseline of peak glucagon response No difference in the plasma insulin concentration after patch, placebo or smoking. Similarly no differences seen for results of glucose clamp tests baseline hepatic glucose production was greater after smoking than after patch or placebo (11.2 (SEM 0.31), 10.6 (SEM 0.30) and 10.4 (SEM 0.34) umol/kg/min) **Comments** Overall the impairment of insulin action following cigarette smoking takes place at the level of the liver, adipose tisue, and muscle. Nicotine appears to deteriorate glycaemic control in Type 2 diabtes merely by exacerbating insulin resistance Nicotine from a patch reduces that action of insulin but does so to a lesser extent than seen with cigarette smoking **Comparator** **List of adverse events** see above **Comments** N/A	Crossover study-patch, placebo or smoking TNS may represent a 'metabolicly' safe measure to help participants with type 2 diabetes to give up smoking

9.7.1.1.5 NRT Adverse events reported in RCTs - Abuse Potential

Study details	Participant details	Results	Comments
Author, Year Hurt 1995 [65] **Study design** RCT **Intervention details** **Specific intervention** Nicotine gum **Comparator** NA **Duration of therapy** Cessation **Duration of follow-up** 6 weeks	**Number of participants** n = 26 (divided between tapering regimes) **Inclusion/exclusion** Smokers who had achieved abstinence from smoking but were still using nicotine gum (2 mg) at least 6 months after starting **Baseline characteristics** Median age: 52 years (range 38-62 years) Median use of nicotine gum: 10 pieces/day (range 1 - 24) for a median of 36 months (range 14 - 56). 27% reported having tried to give up nicotine gum use **Proportion of participants reporting an adverse event** NA	**List of adverse events** Participants were randomised to abrupt withdrawal of nicotine gum, tapering with active gum, or tapering with placebo gum At the end of six weeks the proportion of participants who had not relapsed to gum or smoking were 67% (95% CI 29.9-92.5) for the abrupt withdrawal group, 71.4% (95% CI 29.1-96.3) for the taper with placebo gum group, and 60% (95% CI 26.2-87.8) for the taper with active gum group **Comments** N/A	Small sample size and short duration of follow-up limits reliability of findings

Study details	Participant details	Results	Comments
Author, Year West 2000 [68] **Study design** RCT **Specific intervention** Nicorette gum 2 or 4 mg (n=127); Nicorette transdermal patch 15 mg/16 hour patch (n=124); Nicorette nasal spray (n=126); Nicorette inhaler (n=127) **Comparator** None **Duration of therapy** Up to 14 weeks **Duration of follow-up** 15 weeks	**Number of participants** n = 504 **Inclusion/exclusion** Aged 18 years or older; smoked 10 or more cigarettes per day; motivated to give up smoking; good general health and not being treated for a psychiatric disorder; had not tried to give up smoking using NRT in the previous 3 months; no contraindication to any of the NRT products **Participant characteristics** Not reported **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** Study looked at the abuse potential of NRT according to the following measures (gum; patch; spray; inhaler): Mean (SD) amount of product used since last visit, week 15: 2.5 (2.6); 0.3 (0.2); 4.8 (4.0); 1.0 (1.3). Pleasantness/unpleasantness (and satisfaction) compared with cigarettes (week 4): 5 (3.2); 6.5 (3.8); 4.6 (4.0); 5.2 (4.0) How dependent they were on their product (week 15) %: 22%; 0%; 20%; 33% Proportion of participants still using NRT at week 15: 7%;2%; 10%; 7% **Comments** N/A	

9.7.1.1.6 NRT Adverse events reported in RCTs - Cutaneous reactions

Study details	Participant details	Results	Comments
Author, Year Jordan 1992 [66] **Study design** RCT **Intervention details** **Specific intervention** Nicotine patch (2.5cm2, 12.5 mg nicotine, 3.8 mg/24h, each patch for 48 hours **Comparator** NA **Duration of therapy** 42 days, 2 week washout, 4 day study **Duration of follow-up** Acute study	**Number of participants** Intervention: n = 230 (n =186 completed phase 1 and entered and completed phase 2) **Inclusion/exclusion** Healthy men and women smokers, aged 18-65yrs. Exclude: pregnant or lactating; significant medical condition; significant dermatologic disorder. Participants were required to discontinue the use of corticosteroids, antihistamines, and other immune system modifiers. Also excluded if their skin colour would interfere with scoring of skin irritation **Baseline characteristics (n=186)** Sex: 138/186 F Mean (SD) age: 38.2 (11.1) (The demography of the 44 that withdrew early was not different) **Proportion of participants reporting an adverse event** NA	**List of adverse events** Phase 1. Participants wore patches for 42 days. The percentage of participants showing no reaction, faint erythema, or moderately intense erythema with each patch is given. The % with no reaction to the patches ranged from 8.6 to 58.1%. The % with faint erythema ranged from 41.9 to 90.9%, and that with moderately intense erythema ranged from 0.0 to 2.7%. There were no reports of any more severe erythema Phase 2. Contact sensitisation occcurred in three cases with the active patch, but with none with the placebo patch. Otherwise skin scores reflected those of Phase 1, with less than 2% of the skin sites having a reaction other than faint erythema ad less than 1% having pustules or papules Itching was reported by 63% of participants (5% severe); burning by 7% (1% severe). Tingling, or Soreness were each reported by less than 2% and stinging was reported by less than 1% of participants, with no severe reports **Comments** Study indicates that transdermal nicotine has a low potential for contact sensitisation and skin irritation	Study used 48 hour patches not the 16 or 24 hour application used with commercially avavilable ones. Skin reactions possibly greater in this study than with shorter duration patches

9.7.1.1.7 NRT Adverse events reported in RCTs - Body weight

Study details	Participant details	Results	Comments
Author, Year Nordstrom 1999 [67] **Study design** RCT **Specific intervention** Nicotine gum 2 mg or 4 mg, 9-15 pieces per day for 2 months **Comparator** Placebo **Duration of therapy** 2 months **Duration of follow-up** 1 year	**Number of participants** Intervention: n = 75 (2 mg n=35; 4 mg n=40) Comparator: n = 17 **Inclusion/exclusion** Participants had stopped smoking using nicotine gum (2 or 4 mg) or placebo and were abstainers at 1 year. Of the initial sample of 608 there were 92 eligible for this analysis at 1 yr. Participants were at least 20 years of age and in good health **Participant characteristics** Mean age: 43 to 45 years Number of cigarettes smoked per day 21.5 to 24.3 with no difference between those in the placebo, 2 mg or 4 mg groups groups comparable for age, gender, race and smoking habits **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** BMI: baseline; change after 1 year Nicotine gum 2 mg: 25.3 (SD 4.3); 1.2kg/m2 Nicotine gum 4 mg: 28.2 (SD 6.2); 1.3kg/m2 For those still using the gum at 3 months the mean increase in BMI was 1.8 in those using placebo compared to approximately 0.5 in the two nicotine gum groups, but by one year the difference has been eroded **Comments** N/A **Comparator** **List of adverse events** BMI: baseline; change after 1 year 26.7 (SD 5.7); 1.2kg/m2 **Comments** N/A	This present paper is a follow-up of Doherty 1996[515] in which the same group of participants had been followed for only three months

9.7.1.1.8 NRT Adverse events reported in RCTs - Endothelial function

Study details	Participant details	Results	Comments
Author, Year Neunteufl 2001 [56] **Study design** RCT (observer-blinded crossover study) **Specific intervention** Nicotine nasal spray (1 mg) **Comparator** Cigarettes (1 mg nicotine, 12 mg tar) **Duration of therapy** 20 mins **Duration of follow-up** Concurrent with study	**Number of participants** Intervention: unclear Comparator: unclear **Inclusion/exclusion** Total 16 healthy smokers **Baseline characteristics** Not reported. **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**Intervention** **List of adverse events** NA Flow-mediated dilation of the brachial artery was more pronounced after the cigarette than after the spray (found by ANOVA, p=0.017). **Comments** The authors conclude that nicotine alone causes acute endothelial dysfunction, but to a lesser extent than cigarettes. **Comparator** **List of adverse events** NA **Comments**	

9.7.1.2 NRT Adverse events reported in non-randomised controlled studies

9.7.1.2.1 NRT Adverse events reported in non-randomised controlled studies - Cardiovascular

Study details	Participant details	Results	Comments
Author, Year Benowitz 1993 [72] **Study design** Non-RCT (cross over) **Specific intervention** Nicotine patch **Comparator** Cigarette smoking or placebo patch **Duration of therapy** 5 days **Duration of follow-up** Single assessment	**Number of participants** Intervention: n = 12 Comparator: n = 12 **Inclusion/exclusion** Healthy smokers **Participant characteristics** Healthy smokers **Proportion of participants reporting an adverse event** Not reported	**Intervention** **List of adverse events** The nicotine patch did not produce the effects of platelet activation seen with cigarette smoking **Comments** Crossover study of the effects of nicotine on eicosanoid formation. The nicotine levels achieved with the nicotine patch were comparable with those achieved by cigarette smoking **Comparator** **List of adverse events** Cigarette smoking increased the urinary excretion of 11-dehydro-thromboxane B2 and increased plasma concentrations of the platelet alpha-granule constituents platelet factor IV and beta thromboglobulin indicating in vivo platelet activation. These effects were statistically significantly different from those seen with the placebo patch **Comments** N/A	Authors state: "These results suggest that nicotine alone is not responsible for platelet activation seen with cigarette smoking and that the use of the nicotine patch in smoking cessation tretament of patients with ischaemic heart disease is likely to be safer than smoking"

Study details	Participant characteristics	Results - Intervention	Comments
Author, Year Netscher 1995[70] **Study design** Non-randomisd, controlled, crossover study	**Number of participants** Intervention: n = 30 Comparator: n = 30 **Inclusion/exclusion** Healthy volunteers who were habitual smokers **Baseline characteristics** Mean age: 48 years (range 36-72) Sex: 25/30 M **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**List of adverse events** No significant effect on oxygen saturation, carboxyhaemoglobin, catecholamine concentrations, plasma osmolality, vasopressin or fibrinogen concentrations, haematocrit, or white cell or platelet counts, compared with control of 48 hrs smoking abstinance Relative blood flow was significantly decreased with patch compared with non-smoking control ($p < 0.05$), but was not significantly different from smoking. Average heart rate was significantly increased compared with non-smoking control, ($p < 0.05$), but was not significantly different from smoking BP was significantly increased over non-smoking control, ($p < 0.05$), but was not significantly different from smoking **Clinical significance** The acute haemodynamic and haematological effects of smoking are greater than those of nicotine patch. However, the smaller decrease in digital blood flow observed for the patch compared with smoking may be sustained over a more prolonged period due to slower release of nicotine **Comments**	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Zevin 1998 [71] **Study Design** Non-RCT **Intervention details** **Specific intervention** 0, 21, 42 and 63 mg/24 hr transdermal nicotine **Comparator** None **Duration of therapy** 21 days; 5 for each (smoking during 1st 4 days) **Duration of follow-up** Concurrent with study	**Number of participants** n = 12 **Inclusion/exclusion** Healthy male smokers with no interest in stopping smoking, who smoked at least 20 cigarettes per day and whose plasma cotinine levels were at least 150 ng/ml Exclude: Chronic illness, medication use, drug abuse or use of alcohol in excess of 30 gm/day. Study conducted in hospital **Baseline characteristics** Mean (SD) age: 41 (6) years Mean (SD) cigarettes/day: 29 (9) Mean (SD) plasma cotinine levels: 340 (88) **Proportion of participants reporting an adverse event** NA	**List of adverse events** Urinary epinephrine excretion increased with nicotine dose on the non-smoking day ($p < 0.05$) Heart rate, DBP and SBP measured over 24 hours did not differ across the treatments Effects unlikely to be of any significance given the small sample size and difficulty involved in acurate 24 hr urine measurements **Comments**	Heart rate and systolic and diastolic BPs over 24 hrs did not vary significantly with transdermal nicotine dose. Nicotine dose had no significant effect on urinary aldosterone or cortisol excretion. There were no significant changes in hematocrit, white blood cell count, fibrinogen level or lipid profile across the different patch doses High dose nicotine treatment, even with concominant smoking, caused no acute adverse cardiovascular effects

9.7.1.3 NRT adverse events reported in uncontrolled studies

9.7.1.3.1 NRT adverse events reported in uncontrolled studies - Incidence

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Fredrickson 1995 [73] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Transdermal nicotine patch (4wks on 44 mg/day) **Comparator** None **Duration of therapy** 4 weeks **Duration of follow-up** 4 weeks	**Number of participants** n = 40 **Inclusion/exclusion** Heavy smokers **Baseline characteristics** Mean (SD) age: 32.4yrs (9.8) Sex: 20/40 M Mean smoking rate: 32.4 cigarettes/day Mean years smoking: 28.8 Mean Fagerstrom score: 7.3 15% had previously tried to stop smoking at least 5 times **Proportion of participants reporting an adverse event** NA	**List of adverse events** Mention skin reactions but are not specific during which dose period: Erythema only 52.5%; Erythema with edema 15.0%; Erythema with vesicales 5.0%; Bullae/erosions 2.5%; Itching only 7.5% Mention other minor AEs (mild, self-limiting cardiovascular symptoms - tight chest, racing heart, lightheadiness; nausea; vomiting; headache) but do not give absolute values or % values for number of participants Period of 44 mg dose: Difficulty sleeping, 13 (32.5%); Vivid/unusual dreams, 9 (25%); Papillary carcinoma 1 (2.5%) Period of 22 mg dose: Difficulty sleeping, 3 (7.5%); Vivid/unusual dreams, 1 (2.5%); Myocardial infarction, 1 (2.5%) **Clinical significance** Mild cardiovascular symptoms were not clinically significant. No comment on the other Aes **Comments** None	Authors do not report absolute numbers of % of participants suffering from the AEs in a number of cases Uncontrolled study where all participants were given 44 mg/day patches for 4wks immediately followed by 22 mg/day patches for 4wks Data poorly presented

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Gourlay 1999[74] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine patch 21 mg (24 hour), reducing to 14 mg after 4wks, 7 mg at 8 wks and none after 12 wks (also included brief counselling and booklet.) **Comparator** None **Duration of therapy** Unclear **Duration of follow-up** Unclear	**Number of participants** n = 1481 (follow-up on 1392) **Inclusion/exclusion** Aged 18 to 70 with a strong desire to quit smoking, had smoked at least 15 cigarettes daily for the previous three years. Participants taking medication that might interfere with nicotine withdrawal symptoms were excluded from the study **Participant characteristics** Mean (SD) age: 41 (11) years Sex: 56% F Mean (SD) cigarettes per day: 32 (12) **Proportion of participants reporting an adverse event** 1090/1392 participants reported adverse events that were at least possibly related to the use of the nicotine patch	**List of adverse events** Any cutaneous application site reaction 478/1392 Erythema 205/478 (14.7%) Rash 72/1392 (5.2%) Pruritus 289/1392 (20.8%) Irritation 65/1369 (*4.7%) Vesicles 68/1392 (4.9%) Oedema 53/1392 (3.8%) Musculoskeletal ache related to application site 97/1392 (7%) Any sleep problem 669/1393 (48.1%) Dreaming 414/1392 (29.7) Other sleep disturbance 447/1392 (32.1) 36/1392 (2.6%) serious cutaneous reactions were reported. 61/1392 participants reported serious sleep problems **Comments** Application site reactions were reported more often by participants who were younger, had a history of skin disorder, born outside Australasia, or had a university or trade school education, but these associations were modest. (adjusted hazard ratios 0.8 to 1.8). There was no association between pre-existing skin disorders and moderate-severe application site reactions (Hazard ratios <1.3, p>0.3) Predictors of sleep problems associated with the use of the nicotine patch were female gender, smoking cessation by week 4, and high nicotine dependence levels. Concurrent smoking in the first 4 to 14 days of patch use was associated with lower rates of sleep problems (28% vs. 39, p<0.001) compared with individuals who did not smoke, but headache was increased (20% vs 13%, p<0.01) Combined use of patch and smoking did not commonly result in substantial increases in nicotine intake (18/321 (5.6%)). Those who did have a substantial increase in nicotine intake reported statistically significantly more adverse events that were possibly related to nicotine, specifically dizziness/lightheadedness	Conclusions: sleep problems appear to be associated with nicotine withdrawal rather than the use of the patch. They were more common than application site reactions and appeared sooner. There appears little additional risk of moderate-severe application site recations in participants with a history of skin disorders

Study details	Participant characteristics	Results	Comments
Author, Year Hurt 1998 [75] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine nasal spray 1 to 2 mg/hour **Comparator** None **Duration of therapy** 7 days **Duration of follow-up** 7 days	**Number of participants** n = 50 **Inclusion/exclusion** Smokers **Baseline characteristics** Sex: 27/50 M Mean (SD) age: 43.7 (11.5) years Mean (SD) no. of cigarettes smoked per day: 28.5 (11.3) (range 15-65), Mean (SD) no. of years smoking: 22.5 (10.3) Mean (SD) Fagerstrom score: 10.3 (1.5) 90% had tried to give up smoking before **Proportion of participants reporting an adverse event** Not reported	**List of adverse events** Scores reported for specified symptoms (baseline; mean for days 1-7) Runny nose 0.1; 1.3 Nasal irritation 0.1; 1.2 Throat irritation 0.2; 1.0 Watering eyes 0.1; 0.9 Sneezing 0.2; 0.8 Alertness 1.6;1.2 Calmness 1.6;1.1 High feeling 0.8; 0.7 Coughing 0.8; 0.6 Sweating 0.8; 0.5 Headache 0.4; 0.4 Light-headedness <0.1; 0.2 Nausea <0.1; 0.1 Dizziness <0.1; 0.1 Pounding heart 0.1; <0.1 Cold hands and feet <0.1; <0.1 Symptoms reported by 10% or more of participants were headache (n=17), burning sensation on nose, throat or unspecified areas (n=14), watering eyes (n=13), nasal irritation (n=12), throat irritation (n=12), sneezing (n=9), runny nose (n=9), cough (n=7), and awakening during the night or early awakening (n=5). One patient suffered a stroke (72 yr old female). One patient experienced exacerbation of old emotional problems and one participant experienced abdominal pain and subsequently underwent cholecystectomy. Latter two events not considered to be related to the use of spray **Comments** The most frequent adverse experiences were headache, burning sensation, watering eyes, nasal and throat irritation and sneezing	

Study details	Participant characteristics	Results – intervention	Comments
Author, Year House 1995 [78] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine patch, 22 mg tapering down to 11 mg **Comparator** None **Duration of therapy** 8 weeks **Duration of follow-up** 6 months	**Number of participants** n = 22 **Inclusion/exclusion** Adolescent Smokers **Baseline characteristics** Sex: 68% F Mean (SD) age: 15.9 (1.3) years Mean (SD) no. of cigarettes/day: 23.3 (5) Mean (SD) years smoking: 2.6 (1.6) **Proportion of participants reporting an adverse event** NA	**List of adverse events** 59% of participants reported a skin reaction. The worst skin reactions reported during the 8 weeks of therapy were erythema (46%); erythema and oedema (4%); erythema and vesicles (9%) Other adverse events were headaches (41%), nausea/vomiting (41%), dizziness (27%), tiredness (27%) and arm pain (22%) None of these were considered serious or life threatening nor led to the discontinuation of patch therapy **Comments** Nicotine patch apparently safe and well tolerated in adolescents	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Bende 1998 [76] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine nasal spray 0.5 mg per shot (1 mg per dose) Note: dosage of nasal spray was one dose per hour for the first week, then ad libitum thereafter, with gradual reduction encouraged. 79% still used the spray at the 20 week visit **Comparator** None **Duration of therapy** up to 20 weeks **Duration of follow-up** 20 weeks	**Number of participants** n = 40 **Inclusion/exclusion** Over 18 years of age, with a well documented history of chronic rhinitis and/or chronic sinusitis and had smoked at least 15 cigarettes per day for more than 3 years **Baseline characteristics** Mean age: 45 (range 26 to 71) Sex: 17/40 M Mean (SD) cigarettes/day: 22 (6) Mean (SD) years smoked: 28 (10) **Proportion of participants reporting an adverse event** Not reported	**List of adverse events** Incidences % at week 1; week 6; week 20 Nasal irritation: 78; 51; 51 Bleeding in the nose: 22; 21; 20 Irritation in the throat: 62; 30; 10 Sneezing: 78; 51; 65 Irritation in the eyes: 58; 18; 28 Cough: 54; 27; 17 Nausea: 25; 6; 10 Sweating: 47; 28; 17 Headache: 47; 24; 17 Acoustic rhinometry was evaluated by minimal cross sectional area and nasal volume. No clinically significant change was seen compared to baseline. Nasal expiratory peak flow increased significantly ($p<0.01$) by 52 l/min from initial baseline of 249 l/min Smell test score decreased by 0.14 at week 20 compared with baseline (NS). Nasal cytology: 19/29 evaluable participants showed an improvement; 5/29 showed no change; and five showed a deterioration **Comments** 38% of participants were abstainers at week 12 and 35% at week 20. Numbers not reported in paper so attrition and dropouts due to AEs not known	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Bjornson-Benson 1993 [77] **Study design** Uncontrolled study. Population consisted of participants from an RCT: only those previously randomised to NRT and who had continued to use NRT for one year were included in this uncontrolled study. **Intervention details** **Specific intervention** 2 mg nicotine gum **Comparator** **None** **Duration of therapy** Up to 12 months **Duration of follow-up** **12 months**	**Number of participants** n = 3923 **Inclusion/exclusion** Participants were those who entered the Lung Health Study (LHS) and were randomised to special intervention (SI) rather than usual care. All participants in the study were aged 35-60, with mild to moderate airflow obstruction (FEV,/FVC less than or equal to 7). Patients were excluded if they had a lung condition which affected lung function or if they were unlikely to participate in the 5-year follow-up **Participant characteristics** Sex: 63% M, Mean age: 48 years. Participants smoked on average 31 cigarettes/day **Proportion of participants reporting an adverse event** Not reported	**List of adverse events** Mouth iritation 9.2%; Dental problems 8.8%; Mouth ulcers 8.1%; Indigestion 5.4%; Hiccups 4.3%; Throat irritation 2.9%; Jaw ache/problems 2.4%; Nausea 2.2%; Belching 1.3%; Other 16.8% No information on the Adverse events reported by gum users who didn't achieve abstinence **Comments** N/A	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year McNabb 1984 [79] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine gum (2 or 4 mg) **Comparator** NA **Duration of therapy** 6 mths **Duration of follow-up** Not stated	**Number of participants** n = 69 **Inclusion/exclusion** Fifty patients selected because they abstained from smoking whilst using nicotine gum and had at least 4 determinations of their plasma nicotine. Nineteen patients selected from a group of non-abstinent participants because they gave evidence of smoking and chewing gum on the same day and also had several plasma nicotine measurements **Baseline characteristics** Mean age: 47 years (range 29-67) Sex: 35/69 M Mean no. smoking years: 27 Mean (SD) no. cigarettes/day: 34 (12.6) Mean nicotine yield of cigarettes smoked: 0.91 (range 0.20-1.78) **Proportion of participants reporting an adverse event** NA	**List of adverse events** Mean plasma nicotine levels: smoking: 35 ng/ml 2 mg nicotine gum (chewing mean of 9 pieces daily): 9 ng/ml 4 mg nicotine gum (chewing mean of 12 pieces daily): 23 ng/ml Small (unspecified) number of patients allowed unlimited gum use chewed 14-24 pieces of 4 mg nicotine gum daily and achieved plasma nicotine levels higher than their smoking levels **Clinical significance** gum dose should be controlled if plasma nicotine levels are to fall rather than rise on smoking cessation therapy **Comments**	Stated aim of the study is 'to test the hypothesis that persons who chew nicotine gum as desired to control symptoms of withdrawal from smoking maintain levels of nicotine in the plasma that rarely excede those produced by their smoking'. However, only 11 of the studies 69 participants were allowed to chew 'as desired' and their plasma nicotine levels are not reported in detail. Study classified as incidence but no adverse event data reported.

9.7.1.3.2 NRT adverse events reported in uncontrolled studies - Cardiovascular events (healthy subjects)

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Sarabi 2000 [84] **Study design** Uncontrolled study **Specific intervention** Nicotine gum (Nicorette, 4 mg) **Comparator** No real comparison between tretaments made. Smoking one cigarette (0.9 mg nicotine) over 4-5min **Duration of therapy** 30 minutes **Duration of follow-up** 30 minutes	**Number of participants** Intervention: n = 16 Comparator: n = 16 **Inclusion/exclusion** Young (20-25yrs) healthy participants who were regular smokers. None of the participants was taking regular medication or had a history of any disease known to affect the cardiovascular system, or any metabolic or other serious disease. **Baseline characteristics** Sex: 7/16 M More than 10 cigarettes/day: 4/16 5 – 10 cigarettes/day: 6/16 Less than 5 cigarettes/day: 6/19 Mean (SD) duration of smoking: 5 years (3) All participants had fasted overnight and abstained from smoking for at least 8 hours before the study. Measurements were made with the participants in a supine position in an air-conditioned room at a constant temperature of 20 degrees C **Proportion of participants reporting an adverse event** Intervention: Not reported, specific short term effects only Comparator: Not reported, specific short term effects only	**List of adverse events** Nicotine gum increased mean arterial pressure (MAP), heart rate and cardiac index (CI) significantly ($p<0.05$ for all), but not resting forearm blood flow (FBF), resting forearm vascular resistance (FVR) , or total peripheral resistance index (TPRI) No significant changes in FVR during infusion with vasodilatory drug were observed after chewing the gum The index of endothelial function (ratio of FVR with vasodilatory drug given in baseline phase) changed significantly during chewing the nicotine gum ($p<0.01$ for early phase and $p<0.05$ for plateau phase) **Clinical significance** P values given above **Comments** N/A **Results comparator** **List of adverse events** Mean arterial pressure (MAP), cardiac index (CI) and resting forearm blood flow (FBF) changed significantly during smoking. An increase was seen in all of these variables in the early but not plateau phase of smoking ($p<0.01$) as compared to control baseline values. Heart rate increased, compared to baseline, at both early and plateau phases ($p<0.01$ and $p<0.05$ respectively). Resting forearm vascular resistance (FVR) and total peripheral resistance index (TPRI) remained unchanged during both the early and plateau phases The index of endothelial function (ratio of FVR with vasodilatory drug given in baseline phase) changed significantly during smoking ($p<0.01$ for early phase, $p<0.05$ for plateau phase) Clinical significance P values given above Comments **None**	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Stein 1996 [85] **Study design** Uncontrolled study	**Number of participants** Intervention: 54 Comparator: own controls **Inclusion/exclusion** Smoking at least 1 pack/day for at least 1 year, and had made at least one prior attempt to quit; no history of myocardial infarction, angina, hyperthyroidism, excessive alcohol consumption, diabetes or asthma requiring drug treatment. Exclude: Active peptic ulcer disease, pregnant or of child bearing age and not using adequate contraception, or already using nicotine gum All participants began "Freedom From Smoking" classes at the American Lung Association **Baseline characteristics** Sex: 22/54 M Mean (SD) age: 43 years (12) **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**List of adverse events** ECG recordings from those participants who achieved total abstinence throughout the study demonstrated that HR decreased and HRV (variability) increased as participants switched from smoking to patch and again from patch to smoking. Note HRV is a non-invasive measure of autonomic tone) Use of the 21 mg transdermal nicotine patch reduced heart rate and increased HRV **Comments** NA	20/54 participants provided recordings after completion of 10 wks of treatment. 4/54 participants discontinued use of the patch before the 2nd recording, a final smoke-free recording was obtained 4wks after discontinuation of the 21 mg patch
Intervention details		**Results – comparator**	
Specific intervention 21 mg, 14 mg, 7 mg transdermal nicotine patches (Nicoderm) **Comparator** Smoking (baseline); quitting smoking **Duration of therapy** 10 wks (21 mg, 6wks; 14 mg, 2 wks; 7 mg, 2wks) **Duration of follow-up** 14 wks (4wks following cessation of patch use)		**List of adverse events** See above Breath frequency 0.266 (SD 0.040) Hz; 0.248 (SD 0.033) Hz (p=0.009 compared to baseline) **Comments** N/A	

9.7.1.3.3 NRT adverse events reported in uncontrolled studies - Cardiovascular events (subjects with heart conditions)

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Mahmarian 1997 [86] **Study design** Uncontrolled study **Intervention details** **Specific intervention** 14 mg and 21 mg nicotine patches (Nicoderm) **Comparator** None **Duration of therapy** Minimum 6 days **Duration of follow-up** None (Acute study)	**Number of participants** n = 40 **Inclusion/exclusion** Coronary artery disease on angiography; smoked at least 1 pack of cigarettes per day but strong desire to quit; and had a qualifying abnormal SPECT (at least 5% exercise induced reversible perfusion defect) Exclude: unstable angina, recent (<3 mths) coronary angioplasty or bypass surgery, significant valvular heart disease or intolerance to nicotine preparations **Baseline characteristics** Sex: 32/40 M Mean (SD) age: 55 (10) Mean (SD) years smoked: 40 (12) Mean (SD) cigarettes smoked/day: 31 (11) **Proportion of participants reporting an adverse event** NA	**List of adverse events** Patients had no significant change in any of their treadmill exercise haemodynamic variables (heart rate, systolic BP, diastolic BP and rate-pressure product) from baseline to 14- and 21- mg patch therapy. In the 14 participants who had demonstrated exercise induced ST-elevation, the time to 1mm ST segment depression significantly increased from 352 (132) s at baseline to 436 (121) s on 14 mg patches and 417 (133) s on 21- mg patches ($p<0.01$). Exercise duration was significantly increased in all patients from 452 (123) s at baseline to 472 (116) s on 14- mg patches and 493 (108) s on 21- mg patches ($p=0.014$) A significant reduction in the total exercise-induced perfusion defect size (PDS) ($p<0.001$) was observed from baseline (17.5, 10.6%) to treatment with 14- mg (12.6, 10.1%) and 21- mg (11.8, 9.9%) nicotine patches 11/36 participants had a at least 9% decrease in their total PDS from baseline to 14- mg patch therapy and 10/34 participants from baseline to 21- mg patch therapy. No patient had a at least 9% increase in PDS from baseline values Two patients who did not complete the study protocol had nausea and vomiting on nicotine patches. In one participant, symptoms quickly resolved after stopping 21- mg patches Most common side effects: Skin irritation at the patch site, 12/36; Nervousness and insomnia, 5/36; Altered taste, 5/36; 10/36 participants suffered no side effects **Clinical significance** Authors state: Because cardiac risk is known to be directly related to the extent of exercise-induced PDS, the significant reduction in defect size observed in this study would imply that nicotine patches are safe when used for the purpose of smoking cessation **Comments** N/A	Study did not have the power to detect potential adverse clinical events associated with nicotine patch therapy

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Nitenberg 1999 [87] **Study design** Uncontrolled study **Intervention details** **Specific intervention** 4 mg nicotine gum (Nicorette) **Comparator** NA **Duration of therapy** Single dose **Duration of follow-up** Acute	**Number of participants** n = 17 **Inclusion/exclusion** Undergoing diagnostic coronary angiography for evaluation of chest pain; > 50% luminal diameter narrowing of at least one major coronary artery; past chronic cigarette smokers (> 20/day for > 10 years, stopped smoking for at least one year); all drugs that may alter coronary vasomotion (B-blocking agents, calcium antagonists, long-actong nitrates, molsidomine, ACE inhibitors) were discontinued 7 days before the investigation Exclude: History suggestive of unstable angina or MI; congestive heart failure; chest pain during the coronary arteriography **Baseline characteristics** Mean (SD) age, 55 (10) years Sex: 12/17 M **Proportion of participants reporting an adverse event** NA	**List of adverse events** Cold pressure test produced similar increases in arterial presure from baseline, without change in heart rate, before and after nicotine gum Nicotine gum does not apear to acutely reduce the surface area of normal and diseased coronary segments and does not enhance the constricting effect of sympathetic stimulation produced by the cold pressor test **Comments** NRT not a risk for precipitating coronary artery constriction and therefore this is not a reason not to use it in participants with CAD	Small study measuring acute effects only, in ex-smokers

9.7.1.3.4 NRT adverse events reported in uncontrolled studies - Pregnancy

Study details	Participant characteristics	Results – intervention	Comments
Author, Year Ogburn 1999 [90] **Study design** Uncontrolled study **Intervention details** **Specific intervention** 22 mg/24 hr nicotine patch **Comparator** NA **Duration of therapy** 4 days **Duration of follow-up** Concurrent with study	**Number of participants** n = 21 **Inclusion/exclusion** Cigarette smoker, 15 or more per day; third trimester of pregnancy; age 18 or more years; good general health as determined by the study obstetrician; non-high-risk pregnancy (outside of smoking risk); ability to participate fully in all aspects of the study and to provide written, informed consent Exclude: Recent history (preceding 6 mths) of clinically significant heart disease or any other medical condition deemed incompatible with study participation; active chemical dependence on any substance other than nicotine; current psychiatric disorder, or current use of major psychiatric drugs History of serious skin allergies or evidence of severe, chronic dermatosis; current use of other tobacco or nicotine products; previous participation in a nicotine patch study; use of an investigational drug within 30 days of start of study, or current use of clonidine, busporine, doxepine or fluoxetine **Baseline characteristics** Mean (SD) age: 26.5 (5.7) years Mean (SD) gestational age: 27.4 (2.7) wks Mean (SD) current cigarettes/day: 20.5 (8.7) Mean (SD) no. smoking years, 11.0 (6.1) **Proportion of participants reporting an adverse event** NA	**List of adverse events** During the four days of smoking abstinence and nicotine patch use morning foetal heart rates were significantly reduced relative to baseline when smoking ad libitum was permitted Baseline foetal heart rate (morning; afternoon) 142 (SD 7.6); 141.4 (SD 7.0) Day 4 foetal heart rate (morning; afternoon) 135.8 (SD 7.3) (p=0.017 vs baseline); 143 (SD 11.9) (NS vs baseline) Baseline systolic/diastolic ratio (morning; afternoon) 3.7 (SD 1.0); 3.4 (SD 0.7) Day 4 systolic/diastolic ratio (morning; afternoon) 3.5 (SD 0.7); 3.6 (SD 1.2) (NS vs baseline) Baseline % nonreactive (morning; afternoon) 4.6; 4.8 Day 4 % non-reactive (morning; afternoon) 5.0 (NS vs baseline); 0.0 **Comments** No evidence of acute foetal compromise during nicotine replacement therapy	**Study design**ed to assess only acute foetal and maternal effects of nicotine replacement therapy

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Wright 1997 [91] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Single dose 21 mg nicotine patch **Comparator** **None** **Duration of therapy** 8 hrs **Duration of follow-up** 8 hrs Study conducted as inpatients over 21 hrs during which patients abstained from smoking	**Number of participants** n = 6 **Inclusion/exclusion** 27-38 wks gestation; recalcitrant to 'standard care' for smoking cessation; 'Low risk', no obstetric or medical problems and taking no medications except vitamin or iron supplements; singleton pregnancy, normal by ultrasonographic scan; negative CAgE screen for substance abuse; age < 35 years; smoking minimum of one half pack per day **Baseline characteristics** Mean maternal age: 25.7 years (range 21-31 years) Mean weight: 82.05 kg (range 66.1-87.5) (one outlier at 100.7 kg). Mean gestational age: 34.2 wks (range 28.1-37.0) Mean estimated foetal weight: 2288 gm, (range 1185-2736) Smoked 0.5 to 2 packs of cigarettes per day **Proportion of participants reporting an adverse event** NA	**List of adverse events** No measurable differences in foetal well-being observed on placement of the transdermal nicotine replacement system Maternal vital signs remained stable except for predicted drop in pulse the morning after smoking cessation, with gradual rise after placement of patch. No foetal heart rate decelerations or baseline changes and umbilical artery Doppler readings were unchanged. No foetus had clinically significant changes in miute variation, accelerations, or baseline foetal heart rate, nor were there any changes in uterine activity. Ultrasonographic biophysical profiles were unchanged **Comments** Authors comment that the benefits of transdermal nicotine replacement may outweigh the risks of cigarette smoking in pregnancy	Very small study

9.7.1.3.5 NRT adverse events reported in uncontrolled studies - Cutaneous reaction

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Bircher 1991 [82] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine patch, 1%, 10% and 50% and aqueous nicotine 5% **Comparator** **None** **Duration of therapy** 2 and 3 days **Duration of follow-up** Immediate testing	**Number of participants** n = 14 **Inclusion/exclusion** Volunteers who had all experienced cutaneous side-effects from the use of the nicotine patch **Baseline characteristics** Sex: 10/14 M Mean age: 38.6 years (range 23-65 years), Mean no. cigarettes/day: smokers, 12 (range 5-40); ex-smokers, 2 **Proportion of participants reporting an adverse event** NA	**List of adverse events** A positive skin reaction to a component of the patch was seen in 10 participants. Two participants had a contact urticarial reaction to 50% nicotine base, 1 further reacted to all three concentrations, 4 further had equivocal reactions. Only one equivocal reaction was seen with nicotine sulphate. Five participants had a positive allergic reaction to nicotine base. One participant only had a positive reaction to nicotine sulphate, the patch matrix and to the adhesive One Ex-smoker experienced acute tachycardia and sweating after application of 30 mg nicotine base **Clinical significance** **Comments** Three types of reaction identified: irriation due to accumulation of humidity, sweat, bacterial growth under patch – not of great importance due to short term (24 h or less) exposure to each patch; contact urticarial reaction due to local effect of nicotine on the cutaneaous vasculature; contact sensitization to a component of the patch or active ingredient	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Mills 1997 [83] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine patch (16 hour, applied daily, dose not stated) **Comparator** NA **Duration of therapy** 4 weeks **Duration of follow-up** Concurrent with study period	**Number of participants** n = 10 **Inclusion/exclusion** Lifelong smokers Exclude: Pregnancy; significant medical problems; use of medication likely to interfere with the study; history of skin disease atopy or allergy **Baseline characteristics** Sex: 4/10 M Mean age: 35.4 years (range 24-44) **Proportion of participants reporting an adverse event** NA	**List of adverse events** Significant reduction in cutaneous inflamatory response to sodium lauryl sulphate ($p < 0.001$), and irradiation with UV-B ($p < 0.003$) and a reduction in reactive hyperaemia ($p<0.03$) after 2 weeks of treatment which returned to normal at 4 wks. There was no change in blood flow following application of topical nicotinates **Comments** Nicotine delivered by patch transiently suppresses cutaneous inflammatory response	

9.7.1.3.6 NRT adverse events reported in uncontrolled studies - Oral Mucosa

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Wallstrom 1999 [81] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Sublingual nicotine table (2 mg nicotine) **Comparator** NA **Duration of therapy** Up to 6mths **Duration of follow-up** 12 months	**Number of participants** n = 30 **Inclusion/exclusion** Healthy volunteers who were smoking at least 10 cigarettes per day Exclude: Pregnant/breastfeeding women, individuals with pre-existing mouth lesions, acute medical illnesses, history of severe or symtpomatic cardiovascular disease, taking regular psychotropic medication or history of alcohol/drug abuse **Baseline characteristics** Sex: 12/30 M Mean age: 45.2yrs (range 29.3-62.4yrs) M; 39.4yrs (range 25.8-50.6 yrs) F Fagerstrom score >7: 23/30 **Proportion of participants reporting an adverse event** NA	**List of adverse events** Lesions on floor of mouth n=8 participants (all occurred during wks 1-6 and have healed by 6mths). Of those biopsied (n=11) these lesions consisted of keratinised mucosa (n=1), hyperplastic mucosa (n=1), and inflammatory cells present (n=4) Lesions at other sites in the mouth n=15 (baseline) and n=6 at 12mths Other adverse events: The most frequent self-reported adverse events were hiccups (n=13), burni ng/smarting sensation in the mouth and sore throat (n=12), coughing and dry lips (n=7) and dry mouth (n=6) Clinical significance All lesions observed during tablet use were considered clinically non-significant **Comments** N/A	Low-nicotine dependent participants were told to use one tablet/hr up to a maximum of 20 tablets/day; and high-nicotine dependent participants were told to use two tablets/hr up to a maximum of 40 tablets/day During the first week of treatment the daily dose ranged from seven to 38 tablets/day (mean 23) in subjects with a Fagerstrom score of seven or more, and from three to 17 tablets/day in those with a score of less than 7. Compliance at 6wks was high with 90% of participants using at least one tablet a day (mean=23). Mean overall tablet consumption at 6mths was 7 (low-dependency) and 12 (high-dependency) tablets per day The differing consumption of tablets in terms of length of treatment and number of tablets taken per day makes it difficult to assess the treatment effect in terms of adverse events

9.7.1.3.7 NRT adverse events reported in uncontrolled studies - Blood lipid levels

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Moffat 2000 [88] **Study design** Uncontrolled study **Intervention details** **Specific intervention** 22 mg transdermal nicotine patch **Comparator** NA **Duration of therapy** 35 days **Duration of follow-up** 77 days	**Number of participants** n = 43 **Inclusion/exclusion** Not reported **Baseline characteristics** Ex-smokers (n = 27) Mean (SD) age: 45.3 (14.8) M; 38.2 (8.6) F Mean (SD) cigarettes smoked (cig/day): 29.2 (9.2) M; 28.6 (8.5) F Mean (SD) years smoking: 25.7 (8.7) M; 19.7 (7.3) F Nonsmokers (n = 16) Mean (SD) age: 41.9 (11.1) M ; 39.9 (10.8) F **Proportion of participants reporting an adverse event** NA	**List of adverse events** Serum HDL-C; HDL2-C; HDl3-C (mg/dl) (baseline, day 35, day 77) mean (SD) Ex-smokers only Males: 36.0 (3.3), 36.9 (3.4, 42.6 (6.2), p<0.05*; 10.2 (3.1), 10.9 (3.0), 15.5 (3.4), p<0.05*; 25.6 (2.2), 26.2 (2.4) 27.0(4.5) Females: 43.1 (6.0), 42.9 (5.4), 54.3 (6.5), p<0.05*; 14.0 (2.9), 14.2 (3.6), 20.7 (3.6), p<0.05*; 29.4 (5.8), 28.7 (6.5), 33.3 (6.4), p<0.05* * significantly greater than baseline and day 35 Body weight (kg) (baseline, day 35, day 77) mean, SD Males: 73.5 (8.0), 74.0 (7.7), 73.1 (9.0) Females: 65.3 (16.2), 65.7 (17.0), 67.4 (18.1), p<0.05 compared to baseline Total cholesterol (mg/dl) (baseline, day 35, day 77); mean (SD) Males: 197.0 (20.0), 197.6 (18.9), 199.7 (22.5) Females: 197.5 (35.0), 198.9 (36.6), 199.9 (39.4) There was no significant change between baseline and day 35 (day of patch cessation) on any of the measures Authors state: Nicotine administered by transdermal patch inhibits normalisation of HDL-C, HDL2-C and HDL3-C in those who quit smoking, it also prevented weight gain in females. (see general comments) **Comments** N/A	The authors note that the sample size is small (n=43), and that their results conflict with those found in other studies

9.7.1.3.8 NRT adverse events reported in uncontrolled studies - Abuse Potential

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Hatsukami 1993 [80] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine gum 2 mg **Comparator** NA **Duration of therapy** 3 months **Duration of follow-up** 3 months	**Number of participants** n = 128 **Inclusion/exclusion** Smokers of at least one pack per day, no use of other tobacco products, no previous use of NRT gum, motivated to quit smoking, nicotine dependent (DSM-III-R criteria), not receiving treatment for any psychiatric disorder, not alcohol or drug abuser, no current use of psychoactive drugs, not pregnant **Baseline characteristics** Mean (SD) age: 38.3 (9.3) years. Mean (SD) Fagerstrom score: 7.0 (1.5) **Proportion of participants reporting an adverse event** NA	**List of adverse events** A check list of withdrawal symptoms consisted of scores for craving, irritability/anger, anxiety/tension, difficulty concentrating, restlessness, somatic symptoms, hunger, impatience, insomnia, increased eating and drowsinesss. The check list was completed during the last two weeks of gum use and during the week following gum discontinuation. With one month's use of gum the respective mean (SE) scores were 13.6 (1.3) and 13.7 (1.5). With 3 month's gum use the respective scores were 8.7 (1.1) and 10.0 (1.0) The results showed minimal nicotine gum withdrawal symptoms after gum cessation, with virtually no difference in gum withdrawal between the one-month and three-month treatment groups. There was evidence of withdrawal symptoms (difficulty concentrating, increased variablity in reaction-time tests and decreased vigour. Authors concluded that there is minimal physical dependence on nicotine gum **Comments** N/A	

Study details	Participant characteristics	Results – intervention	Comments
Author, Year Schuh 1997 [89] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Nicotine nasal spray (0.5 mg /spray) and nicotine vapour inhaler (0.0013 /inhalation **Comparator** Nicotine from cigarette smoking (0.1 mg per puff) **Duration of therapy** One day **Duration of follow-up** One day	**Number of participants** Intervention: n = 12 Comparator: n = 12 **Inclusion/exclusion** Smoked at least 20 cigarettes per day of a brand containing at least 0.7 mg nicotine /cigarette **Participant characteristics** Smokers who were ovenight deprived of nicotine prior to testing Sex: 9/12 M Mean age: 36 years (range 21 to 45) Mean years of smoking: 18 years (range 5 to 33) **Proportion of participants reporting an adverse event** Intervention: N/A Comparator: N/A	**List of adverse events** Only modest elevations on a measure of good drug effects were observed with either the spray or the inhaler. These delivery systems produced unpleasant effects of burning throat and nose, watery eyes, runny nose, coughing and sneezing **Clinical significance** The limited ability of nicotine via nasal spray or inhalor to produce 'good drug effects' and the unpleasent effects associated with them might be expected to limit the abuse liability. **Comments** N/A	Overall results are consistent with the conclusion that the nicotine nasal spray and vapor inhalor are of substantially lower abuse liability than cigarettes in experienced smokers receiving initial exposure to these products

9.7.1.4 NRT adverse events reported in case-control studies

9.7.1.4.1 NRT adverse events reported in case-control studies - Incidence

Study details	Participant characteristics	Results
Author, Year Kimmel 2001 [92] **Study design** Case-control study of association of MI with NRT patch use **Intervention details** **Specific intervention** Nicotine patch as general use **Comparator** None **Duration of therapy** NA **Duration of follow-up** NA	**Number of participants** Cases: n = 653 Controls: n = 2990 **Inclusion/exclusion** Cases: Smokers admitted to hospital with first MI Controls: Smokers who had not experienced a first MI **Baseline characteristics** NA **Proportion of participants reporting an adverse event** NA	**List of adverse events** only MIs studied 3/653 cases had used a nicotine patch within the 7 days prior to their hospital admission for MI (0.46% this was compared to the patch use in the controls (30/2990 (1%) the Exact OR was 0.46 (95% CI 0.09, 1.47). This finding was adjusted for several cofounders but none of these adjustment had any real effect on the OR and the Cis **Comments** This study did not identify a statistically or clinically significant association between the use of nicotine patches and MI in an unselected population. These findings are consistent with the physiological and pharmacodynamic properties of nicotine patches and with other studies that suggest no serious adverse cardiovascular effects among patch users

9.7.1.5 NRT adverse events reported in surveillance studies

Study details	Participant characteristics	Results
Author, Year Spyker 1996 [93] **Study design** Surveillence, post-marketing Information source: FDA spontaneous reporting system (SRS) for AE **Intervention details** **Specific intervention** Nicotine patch **Comparator** Polacrilex resin (nicotine gum) **Duration of therapy** NA **Duration of follow-up** NA	**Number of participants** Not stated **Inclusion/exclusion** NA **Characteristics** No details given **Number of participants reporting an adverse event** Intervention:1281 (12.3/million Rx) Comparator: 1281 (12.3/million Rx)	**Intervention** **List of adverse events** A total of 3848 adverse events were reported with patch (11.8 adverse events per million participants treated) Dermatologic (local or general), 1533 (130/million treated); Addiction or dependence, 24 (2/million treated); gastrointestinal, hiccups, 522 (44/million Rx); Oral problems, 141 (12/million Rx); Withdrawal, no effect, headache, 442 (38/million Rx); Nervous system, CNS, 384 (33/milliobn Rx); Sleep and dream disturbance, 416 (35/million Rx) **Comments** N/A **Comparator** **List of adverse events** A total of 3848 adverse events were reported with patch (11.8 adverse events per million participants treated. Dermatologic (local or general), 39 (3.2/milliom Rx); Addiction or dependence, 475 (39/million Rx); gastrointestinal, hiccups, 163 (13/million Rx); Oral problems, 289 (23/million Rx); Withdrawal, no effect, headache, 156 (13/million Rx); Nervous system, CNS, 75 (6.1/million Rx); Sleep and dream disturbance, 17 (1.4/million Rx) **Clinical significance** The authors speculate that, since there are no reports of primary nicotine dependence to gum or patch, the higher rate of dependence/addiction seen with gum may be a result of misuse and/or different pharmacokinetics **Comments** Abstract only. Few study details and data. No indictaion of dose regimens associated with AEs nor any participant details

Study details	Participant characteristics	Results - intervention
Author, Year Ottervanger 1997 [94] **Study design** Surveillence (adverse reactions database) 220 Reports of drug-induced chest pain or myocardial infarction received by the Netherlands Centre for Monitoring of Adverse Reactions to Drugs over 20 years (1975-1994) **Intervention details** **Specific intervention** NA **Comparator** NA **Duration of therapy** NA **Duration of follow-up** NA	**Number of participants** Not stated **Inclusion/exclusion** Not reported **Characteristics** NA **Number of participants reporting an adverse event** Nine reports attributed to nicotine	**List of adverse events** Total, 9 (8 with patches, 1 with gum) MI, 5; Chest pain, 4 Nicotine was the second most frequently reported drug. Proportion of drug-induced MI and chest pain attributed to nicotine, 4.1% **Comments** Study was designed to analyse causes of reported drug-induced MI and chest pain rather than specifically to examine the incidence of these AE with nicotine replacement therapy

Study details	Participant characteristics	Results
Author, Year Spyker 1998 [117] **Study design** Surveillence (FDA Medwatch ADE Database) **Intervention details** **Specific intervention** Nicotine patch and gum (all formulations) **Comparator** None **Duration of therapy** NA **Duration of follow-up** NA	**Number of participants** 12.3 million prescriptions for gum + 11.8 million prescriptions for patches **Inclusion/exclusion** Not reported **Characteristics** Not reported **Number of participants reporting an adverse event** Total of 5129 adverse event reports	**List of adverse events** Site reactions: 29.7% of these patch related and a further 24.1% rashes compared to 0.23% with gum and 1.17% rashes All classes of adverse event more common with patch than with gum except for gum problems which were more common with gum. gI related events 3 times more common with patch; 18 times more allergy-related events; five times the number of nervous system related events; psychiatric events such as insomnia, dream abnormalities and nervousness 30 times more frequent with the patch Overall patch 8 times was more likely to be associated with an adverse event than the gum **Comments** Spontaneous AE reports relating to nicotine patch and gum

9.7.1.6 NRT adverse events reported in systematic reviews

REVIEW DETAILS
Author
Greenland 1998[52]
Objective: To estimate the frequency of adverse effects associated with the transdermal nicotine patch.
Inclusion Criteria
Study design: RCTs with at least 20 patients per treatment arm, that presented adverse event data.
Participants: None specified (not all were smokers or using the nicotine patch for smoking cessation).
Intervention: Transdermal nicotine patch
Outcome: Adverse events
Exclusion Criteria: None
Quality Assessment: By restricting studies included to RCTs with at least 20 participants per treatment arm and that presented adverse events data.

RESULTS
Total studies: n = 34
Types of studies: RCT (34) (plus 1 study on contact sensitisation)
Type of smoker: Adults
M/F ratio: 1:1
Level of nicotine dependence: Unclear
Fagerstrom score: Not stated
Specific intervention: Most studies used patches containing 17 to 25 mg, however 4 (365 patients) used patches of 28 mg or more, 10 studies (1793 patients) used patches of 14 or 15 mg, and 2 studies (167 patients) used patches of 7 or 8 mg.
Comparator: Placebo. Usually this was completely inert but some studies (total of 9, with 1155 patients) used placebo patches that contained small doses of nicotine.
Specific outcome: Withdrawals (due to adverse events) and adverse events by body system
Definition of smoking cessation used: NA
Duration of follow-up: Not stated
Settings: Not stated
Participants: Most of the patients included in the studies in the review were middle-aged; with the exception of one study that included only young men the mean age reported ranged from 37 to 56 years with a median age of 45 years. The overall gender balance was near to 1. No pregnant women took part in any of the studies analysed.

Quality of included studies: Not stated

COMMENTS
The literature search was not exhustive in that it only included MEDLINE. It did however include published and unpublished studies from Ciba-geigy. The cutoff date for papers to be included was December 1 1996. So not new data.

9.7.2 Adverse Event Data Extraction Tables - Bupropion

9.7.2.1 Bupropion adverse events reported in RCTs

9.7.2.1.1 Bupropion adverse events reported in RCTs - Cardiovascular events

Study details	Participant details	Results	Comments
Author, Year Braconnier 1983 [120] **Study design** RCT **Specific intervention** Bupropion 150 mg/day or 300 mg/day. High dose could be increased to 450 mg/day **Comparator** Imipramine 25 mg/day, could be increased to 150 mg/d **Duration of therapy** 28 days **Duration of follow-up** 28 days	**Number of participants** Intervention: n = 90 (high dose, n = 45 and low dose, n = 45) Comparator: n = 45 **Inclusion/exclusion** Age 55 or older; total score of at least 18 on the 21-item Hamilton depression scale; diagnosis of non-psychotic, primary depressive disorder **Participant characteristics** Mean age (three treatment groups): 63 to 64 Sex: 45/110 M **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**Intervention** **List of adverse events** Neither low dose nor high dose bupropion had any effect on sinus heart rate, orthostatic blood pressure of main effects on blood cholesterol **Comments** Findings agree with previous data that bupropion has no effect on CV function in younger patients with depression **Comparator** **List of adverse events** Sinus tachycardia, with significant elevation at days 7 and 28. Rate corrected QT interval was significantly prolonged compared to both low and high bupropion tretament ($p<0.04$). No significant effect on PR and QRS intervals Significantly increased the fall in SBP and DBP upon standing compared with either dose of bupropion No significant main effect on serum cholesterol **Clinical significance** **Comments** N/A	

Study details	Participant details	Results	Comments
Author, Year Kiev 1994 [121] **Study design** RCT **Specific intervention** Bupropion 225 - 450 mg/day (ascending regimen) **Comparator** nortriptyline (75-150 mg/d) **Duration of therapy** 6 wks **Duration of follow-up** Concurrent with period of treatment	**Number of participants** Intervention: n = 58 Comparator: n = 57 **Inclusion/exclusion** Outpatients with a diagnosis of non-psychotic major depression which was not superimposed on dysthymia or secondary to a pre-existing condition (medical or psychiatric). All patients were currently in a major depressive episode, not suicidal and suitable for treatment with bupropion Exclude: History or current diagnosis of thyroid disorder, cardiac arrhythmia, serious cardiovascular disease or other unstable medical condition; pregnancy or lactation; clinical history of alcohol or substance abuse; pre-disposition to seizures. Medications prohibited during study: Any psychoactive drug taken within 1 wk of treatment phase (2 wks for monoamiine oxidase inhibitors or protriptyline and 4 wks for fluoxetine or any investigational drug); prior therapy with bupropion or nortriptyline; current therapy with thyroid medication, cimetidine, quinidine, or other class I antiarrhythmic agents **Participant characteristics** Mean age: 46.3 years Sex: 50% M **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** 8/55 patients had orthostatic changes with none reporting symptoms of orthostatic hypotension ECG changes from baseline: Significant decrease of 47.9 (SD 21.6) msec in mean RR interval on day 42 ($p < 0.05$), corresponding to a heart rate increase of 3.3 bpm. Significant decrease in mean QTc interval by the Fridericia formula of 9.4 units on day 42 ($p < 0.05$) Cardiovascular adverse events: dizziness, 0; oedema, 0; faintness, 0; palpitations, 2; tachycardia, 1 **Comments** Orthostatic change defined as a drop of 20 mm Hg after 1 min standing, which was at least 20 mm Hg greater than the orthostatic drop at baseline **Comparator** **List of adverse events** Orthostatic changes, 13/50 participants with 3/13 reporting symptoms Significant difference ($p<0.001$) compared to bupropion on the RR interval (-188.2 (SD 23.4) msec vs -47.9 (s.d 21.6) msec) and the QTc interval (+14.4 (SD 4.1) units vs. -6.4 (SD 3.9) units) on day 42 Significant within treatment difference ($p<0.05$) on day 42 on the QRS interval duration (+4.4 (SD 2.1) msec) Cardiovascular Adverse events dizziness, 1; oedema, 1; faintness, 2; palpitations, 2; tachycardia, 7 ($p<0.05$ compared to bupropion) **Comments** N/A	Trial designed to compare safety of two antidepressents (bupropion and nortriptyline). Not conducted in the context of smoking cesation, hence population of psychiatric patients BP and verbally reported patient experience monitored weekly and ECgs taken at baseline (day 0), day 14 and day 42

Study details	Participant details	Results	Comments
Author, Year Roose 1987 [122] **Study design** RCT **Specific intervention** Bupropion 8 mg/kg maximum dose 450 mg/day Mean daily dose of bupropion was 445 mg (SD 16) (6.8 mg/kg) **Comparator** Imipramine 3.5 mg/kg to a maximum dose Mean daily dose of imipramine reached was 197 (SD 78) (3 mg/kg) **Duration of therapy** 3 weeks **Duration of follow-up** Unclear	**Number of participants** Intervention: n = 10 (1 drop out) Comparator: n = 9 (6 drop outs) **Inclusion/exclusion** Inpatients of an affective-disorder ward requiring tretament with an antidepressant. All patients had a history of conjestive heart failure (CHF) with a large heart by chest roentgenogram (cardiothorasic ratio >1 in the frontal view) **Participant characteristics** Sex: 6/10 F Mean age: 69 years (range 53-78) **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** Baseline ejection fraction (EF) 31% (SD 13.7) (range 19% to 54%), post bupropion EF 32.4 (SD 20.7) Baseline End diastolic volume (EDV) 103.5 (SD 29.8) ; post EDV 113.4 (SD 40.3) Baseline end systolic volume (ESV) 72.4 (SD 36.6); post 81.4 (SD 43.9) Baseline peak sytoloc pressure (PSP)/ESV 2.36 (SD 1.31); post PSP/ESV 2.99 (SD 2.92) Baseline supine systolic blood pressure (SBP) 132 (SD 13) mmHg; post supine SBP 136 (SD 19) Mean orthostatic fall in Bp on bupropion was 2 mmHg Adverse events reported: chest pain (1 participant) **Comments** Bupropion did not have a deleterious effect on left ventricular function, not did it induce orthostatic hypotension **Comparator** **List of adverse events** Baseline ejection fraction (EF) 31% (SD 13.7) (range 19% to 54%), post EF 30.4 (SD 17.1) Baseline End diastolic volume (EDV) 103.5 (SD 29.8) ; post EDV 103.5 (SD 37.5) Baseline end systolic volume (ESV) 72.4 (SD 36.6); post 76.2 (SD 39.4) Baseline peak sytoloc pressure (PSP)/ESV 2.36 (SD 1.31); post PSP/ESV 2.53 (SD 1.98) Baseline supine systolic blood pressure (SBP) 132 (SD 13) mmHg; post supine SBP 129 (SD 16) Mean orthostatic fall in BP on imipramine was 15mmHg Adverse events reported by six participants: five participants had orthostatic hypotension; elevation of liver enzymes (one participant) **Comments** N/A	Study was crossover design with drug tapering at the end of the first treatment and then a 5 day washout before starting second treatment Study indicates that bupropion does not adversely effect LVF

9.7.2.1.2 Bupropion adverse events reported in RCTs - Sexual functioning

Study details	Participant details	Results	Comments
Author, Year Batey 1998 [123] **Study design** RCT **Specific intervention** Bupropion SR (100-300 mg/day) **Comparator** Sertraline (50-200 mg/day) **Duration of therapy** 16 weeks **Duration of follow-up** 16 weeks	**Number of participants** Intervention: n = 122 Comparator: n = 126 **Inclusion/exclusion** Outpatients with moderate to severe depression, in a stable relationship, with normal sexual functioning **Baseline characteristics** Not reported **Proportion of participants reporting an adverse event** Intervention: Not stated Comparator: Not stated	**Intervention** **List of adverse events** A statistically significantly smaller percentage of bupropion patients experienced sexual dysfunction Nausea, diarrhoea, somnolence, and sweating were less common with bupropion **Clinical significance** **Comments** N/A **Comparator** **List of adverse events** A statistically significantly greater percentage of sertraline patients experienced sexual dysfunction. This included orgasm dysfunction and sexual arousal disorder which began as early as day 7 of treatment Nausea, diarrhoea, somnolence, and sweating were more common with sertraline **Comments** N/A	Vital signs and weight assessments were comparable between the two treatment groups

Study details	Participant details	Results	Comments
Author, Year Coleman 1999 [124] **Study design** RCT **Specific intervention** Bupropion SR mean dose 290 mg/day (range 100-365 mg) **Comparator** Sertraline and placebo **Duration of therapy** 8 weeks **Duration of follow-up** 8 weeks	**Number of participants** Intervention: n = 122 Comparator: Sertraline, n = 118; placebo, n = 124 **Inclusion/exclusion** Patients suffering from depression Exclude: Known predisposition to seizure or recieving medications that lower seizure threshold **Baseline characteristics** Mean age: 38 years (range 18 to 74) Sex: 159/364 M **Proportion of participants reporting an adverse event** NA	**Intervention** **List of adverse events** Bupropion SR had no effect on the number of patients with sexual desire disorder compared with placebo The incidence of sexual arousal disorder was low: <1 % at day one to 6% at day 56. No statistically significant difference compared with placebo Orgasm dysfunction day 7, 4% to day 56, 10% (not statistically significantly different from placebo Premature ejaculation: none Satisfaction with sexual functioning: no difference during study between bupropion and placebo **Comments** Analysis used LOCF. Pairwise comparisons of each pair of treatments. Differences tested using ANOVA Attrition from study was high, 22% from bupropion, 32% from placebo and 36% from sertraline Difference primarily due to numbers lost to follow-up and contents withdrawn in different groups **Comparator** **List of adverse events** Sertraline: Results not relevant, therefore not included Placebo: Sexual arousal disorder was low: 3 % at day one to 10% at day 56 Orgasm dysfunction day 7 5% to day 56 14% (not stat. Sig different from placebo) Premature ejaculation: 2-4% **Comments** N/A	Results suggest that bupropion has no adverse effect on sexual function in depressed participants

Study details	Participant details	Results	Comments
Author, Year Labbate 2001 [125] **Study design** RCT **Intervention details** **Specific intervention** Bupropion (300 mg/day) **Comparator** Placebo **Duration of therapy** 14 days **Duration of follow-up** 14 days	**Number of participants** Intervention: n = 13 Comparator: n = 13 **Inclusion/exclusion** Healthy males **Baseline characteristics (n=13)** Mean (SD) age: 30.2 (6.3) years **Proportion of participants reporting an adverse event** Intervention: NA Comparator: NA	**Intervention** **List of adverse events** Sexual function as measured by the CSFQ total score was unchanged during the placebo or bupropion phase of the study (df=2, F=0.361, p=0.701) (baseline 45.4 (SD 4.0), placebo (44.8 (SD 4.0), bupropion 45.2 (SD 3.2). There were no differences in any of the sub-scores during bupropion or placebo either There were no significant differences for bupropion compared to baseline or placebo for any of the measures of penile erectile function **Comments** Findings support that bupropion does not have subjective adverse sexual side effects and does not affect nocturnal erections in healthy men Aim of study was to examine effects on penile erectile function so hence the reporting of loss of interest in smoking as a adverse event **Comparator** **List of adverse events** See above **Comments** N/A	This was a randomised placebo controlled crossover trial where all participants received both of the interventions with a 7-10 day washout period between the two. Of the sixteen men who originally entered the study, two dropped out because of non-compliance with the protocol, and one experienced penile discomfort and bleeding during the baseline measurement period

Study details	Participant details	Results	Comments
Author, Year Segraves 2000 [126] **Study design** RCT **Intervention details** **Specific intervention** Bupropion SR, 100-300 mg/day escalating dose **Comparator** Sertraline, 50-200 mg/day **Duration of therapy** 16 wks **Duration of follow-up** Concurrent with study period	**Number of participants** Intervention: n = 122 Comparator: n = 126 **Inclusion/exclusion** Minimum age 18 years; diagnosis of moderate to severe depression, duration 4 wks to 24 mths; patients were required to be in a stable relationship, have normal sexual functioning, preform sexual activity that could lead to orgasm at least once every 2 weeks, and be willing to discuss their sexual functioning with the investigator. Exclude: Predisposition to seizure; history or current diagnosis of anorexia or bulimia; pregnancy or lactation; clinical history of alcohol or substance abuse within the last year; receipt of psychoactive drug within 1 wk of study (2 wks for MAOIs or protriptyline and 4 wks for fluoxetine or any investigational drug); prior use of bupropion or sertraline; actively suicidal **Baseline characteristics** Bupropion group: Sex: 52% M Mean (SD) age: 39 (10.5) Mean compliance rate, 98% Sertraline group: Sex: 52% M Mean (SD) age: 40 (10.3) (range = 18-74) Mean compliance rate, 99% **Proportion of participants reporting an adverse event** Intervention:NA Comparator: NA	**Intervention** **List of adverse events** Sexual arousal disorder, m = 7%, f = 2% (p=0.02, 0.05 respectively vs. sertraline Premature ejaculation, 5% (NS vs. sertraline); Orgasm dysfunction, m = 10%, f = 7% (p<0.001 vs. sertraline) **Comments** Study examines sexual function in the context of treatments for depression and may therefore not be directly applicable to the use of bupropion for smoking cessation **Comparator** **List of adverse events** Sexual arousal disorder, m = 19%, f = 12%; Premature ejaculation, 0%; Orgasm dysfunction, m = 61%, f = 41% **Comments** Significantly greater sexual dysfunction observed with sertraline-treated patients is not relevant to the context of smoking cessation	Information indicates relative lack of adverse effect of bupropion on sexual functioning

9.7.2.2 Bupropion adverse events reported in non-randomised controlled studies

9.7.2.2.1 Bupropion adverse events reported in non-randomised controlled studies - Cardiovascular events

Study details	Participant characteristics	Results	Comments
Author, Year Wenger 1983[127] **Study design** non-RCT **Intervention details** **Specific intervention** Bupropion 300-750 mg, ascending regimen **Mean maximum daily dose 552 mg** **Comparator** Amytriptyline **Duration of therapy** 6 wks **Duration of follow-up** NA	**Number of participants** Intervention: n = 23 Comparator: n = 23 **Inclusion/exclusion** Depressed inpatients at a Veterans Administration Hospital. **Participant characteristics** Sex: 100% M Mean age: 50 years **Proportion of participants reporting an adverse event** Intervention:NA Comparator: NA	**Intervention** **List of adverse events** Mean (SD) changes from baseline for any of the ECG parameters measured were: PR interval 1.8 (1.7) msec; QRS duration 0.4 (1.1) msec, QTc interval -3.6 (3.5) msec; QRS height 0.3 (0.4); RR interval -30 (19) msec. None of these were statistically significant **Comments** N/A **Comparator** **List of adverse events** Significant prolongation in PR interval compared to Participant and prolongation of QRS duration and decrease in QRS height compared to effect of bupropion **Comments** N/A	Data vs baseline suggests bupropion has little effect on cardiac conduction Comparison with amitrypyline not relevent regarding smoking cessation

9.7.2.3 Bupropion adverse events reported in uncontrolled studies

9.7.2.3.1 Bupropion adverse events reported in uncontrolled studies - Incidence

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Roth 1999[129] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Bupropion SR 150 mg bd **Comparator** **None** **Duration of therapy** 8 weeks **Duration of follow-up** Unclear	**Number of participants** n = 22 **Inclusion/exclusion** Not reported **Baseline characteristics** Sex: 96% M Mean (SD) age: 54 (10.1) years, Smoked mean (SD) of 20.8 (13.0) cigarettes/day. 64% had co-existing medical conditions: hypertension, CAD, COPD 37% were receiving treatment for psychiatirc diagnoses, including depression, post-traumatic stress disorder, and bipolar disorder **Proportion of participants reporting an adverse event** NA	**List of adverse events** Mild adverse effects (dry mouth, insomnia, bad taste in mouth) were noted in 14% of participants One participant with bipolar disorder experienced precipitation of his mania on 150 mg b.i.d. bupropion SR: it was resolved by reducing the dose to 150 mg/day **Comments**	Small sample size from which to make such general conclusions

Study details	Participant characteristics	Results – intervention	Comments
Author, Year van Wyck Fleet 1983 [130] **Study design** Uncontrolled study (data pooled from clinical trials of bupropion) **Intervention details** **Specific intervention** Bupropion 15-1200 mg/day (most common 300-450 mg/day - averages across studies) **Comparator** Placebo or tricyclics (Information on patients who received placebo or tricyclics not extracted as not a proper comparison) **Duration of therapy** 4 to 13 weeks (averages across studies) **Duration of follow-up** 4 to 13 weeks (averages across studies)	**Number of participants** n = 1153 **Inclusion/exclusion** Participants were those enrolled in clinical trials of bupropion (1970-1981). Participants demonstrated normal and/or clinically acceptable values for physical examinations, vital signs, clincial laboratory test (haematology, clincial chemistry, urinalysis), EEg and a baseline evaluation of current symptomatology Concomitant medication, with the exception of chloral hydrate was prohibited., but in three studies antipsychotics were also permitted **Baseline characteristics** Not reported **Proportion of participants reporting an adverse event** NA	**List of adverse events** Percentage of participants withdrawing due to individual adverse events: Excitement/agitation 9.1%; Anticholinergic 5.4%; Miscellaneous 4.6%; Motor disturbance 4.5%; Psychological problems 3.9%; Dermatologic 3.0%; Nausea/vomiting 2.7%; Drowsiness 2.6%; Weight loss 2.4%; Headache/nasal conjestion 2.4%; Thinking difficulties 21.%; Dizziness 1.8%; tachycardia/palpitations 1.4% (Note: Participants may have withdrawn due to more than one event, only adverse events with at least >2% occurrence are included) EEG summary Normal baseline/normal on treatment 86.9%; Normal treatment / abnormal treatment 6.2%; Abnormal baseline/normal treatment 1.5%; Abnormal baseline/abnormal treatment 5.4% Seizures Major motor seizures reported by two healthy volunteers and 8 patients with depression. Two volunteers had seizures after 2 or 4 days of consecutive 800 mg single doses after at least 40 days of treatment at lower doses (upto 550 mg/day). Of the 8 patients who had seizures one had a history and one a possible history of seizure; the dose range was 600-900 mg/day except for one with history of seizure who took 450 mg/day **Clinical significance** **Comments** Only adverse events that resulted in withdrawal of treatment are included in the summary. Also given the relatively small size of the database cut off of 2% for inclusion in this summary must mean many events were not included in this publication	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Davidson 1989 [131] **Study design** Uncontrolled study. Data from previously conducted clinical trials. **Intervention details** **Specific intervention** Bupropion up to 900 mg/day **Comparator** **None** **Duration of therapy** Unclear **Duration of follow-up** Unclear	**Number of participants** n = 4262 **Inclusion/exclusion** Not reported **Baseline characteristics** 4097 were patients and 165 volunteers **Proportion of participants reporting an adverse event** NA	**List of adverse events** 37/4262 reported a seizure Crude overall incidence is 0.87%. 19 seizures occurred at doses above 450 mg/day. The incidence associated with lower doses is 0.35%. The cumulative risk over 2 years is 0.48% up to day 720 if only doses of less than 450 mg/day are considered. At all doses the risk is 1% by Day 180 increasing to 1.74% by Day 720 The dose at which seizures occurred ranged from 100 mg to 9000 mg. There was no consistent relationship between dose escalation and occurrence of a seizure. The length of time participants received the dose of bupropion at the dose at which the seizure occured ranged from 1 to 281 days (mean 8 days), with 21 cases being on that dose for 15 days or less For the 21 cases for whom the information was available, 77.3% of sezures occurred within 240 minutes of a dose of bupropion **Clinical significance** 11/1802 (0.61%) males suffered seizures compared with 23/2457 (0.93%) females (NS). There was no association between seizure risk and age Predisposing factors: 14 patients were considered to have predisposing factors: 4 history of seizure (1 plus head trauma); 1 metastatic brain carcinoma, 1 undergoing alcohol withdrawal, 1 head trauma, 5 receiving concomitant medication known to lower the seizure threshold, 2 not stated **Comments** Of the 4262 participants exposed to bupropion the dose breakdown was : < 150 mg/day n= 381; 150-300 mg/day n=1072; 301-450 mg/day n=1943; 451-900 n=866 Duration of use of bupropion: < 1 week n=323; 1-4 weeks n=1161; 5-8 weeks n=889; 9-12 weeks n=387; 13-26 week n=608; 27-52 weeks n=304; 53-104 weeks n=351; > 104 weeks n=239	

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Peck 1983 [179] **Study design** Uncontrolled retrospective cohort study **Intervention details** **Specific intervention** Bupropion 450-900 mg/day **Comparator** **NA** **Duration of therapy** Not stated **Duration of follow-up** Not stated	**Number of participants** **NA** **Inclusion/exclusion** **Baseline characteristics** All healthy participants or patients who experienced a convulsion during treatment or experiment with bupropion in N. America **Proportion of participants reporting an adverse event** NA	**List of adverse events** **Clinical significance** **Comments** Summary of bupropion associated seizures. Exactly the same data as included in van Wyck Fleet [130]	Exactly the same data as included in van Wyck Fleet [130]

Study details	Participant characteristics	Results – intervention	Comments
Author, Year Dunner 1998[132] **Study design** Uncontrolled cohort study (prospective over 105 sites) **Intervention details** **Specific intervention** Bupropion SR 50 mg bd to 150 mg bd **Comparator** **None** **Duration of therapy** 8 weeks extended up to 1 year in some patients **Duration of follow-up** 8 weeks to 1 year	**Number of participants** n = 3100 (3094 included in seizure rate calculation) **Inclusion/exclusion** Patients with DSM-III-R diagnosis of depression without a current or past diagnosis of an eating disorder, or any history or family history of seizure **Baseline characteristics** Mean (SD) age: 42 (12) (range 18-86) Sex: 1933/3100 F Major depression: 2304/3100 (74.3%) **Proportion of participants reporting an adverse event** NA	**List of adverse events** n=3094 (6 had had bupropion before) None of the 6 excluded suffered a seizure 3/3094 participants experienced a seizure; 2 within the first 8 weeks. In this period the observed incidence rate was 0.06% (upper 1-side CI 0.14%). The observed seizure rate for the whole study period (1 year) was 0.10% (upper 1-side CI 0.19%). In participants who consumed therapeutic dose of bupropion (n=2958) the survival analysis yielded a cumulative seizure rate of 0.08% (upper 1-sided Ci 0.18%) for the acute phase and 0.15% (upper 1-sided 95% CI 0.30%) for the whole follow-up Other serious AEs that were reported included suicide attempt or overdose (9), accidental injury (4), myocardial infartcion (3, all who had preexisting cardiovascular pathology). There were also six deaths (three suicides, 2 cardiac complications, 1 homicide). The events precipitating these deaths were not considered related to bupropion SR 84% of participants who received at least one dose of bupropion SR did not experience an adverse event that significantly interfered with functioning **Clinical significance** Dose of bupropion at which seizure occurred were 300 mg/day; 300 mg/day and 150 mg/day giving mg/kg doses respectively of 4.2, 3.5 and 1.1 **Comments** 2057 (66%) completed the 8 week acute phase and 1577 (77%) of these entered the continuation phase All three participants with seizures experienced a single generalised seizure characterised by sudden loss of consciousness and tonic or tonic-clonic contractions. There were clear predisposing factors in 2 of the 3: alcohol withdrawal 11 years previously; loss of consciousness in a motor accident and possible alcohol abuse. In addition the third participant had a history of alcohol abuse, although no evidence of recent alcohol use In addition to these three reports of seizure there was one report of a patient who collapsed, but for whom confirmi mg evidence of a seizure is not available. Furthermore there were two cases associated with bupropion overdose There were also three cases that appeared unrelated to bupropion use	If you include all cases there were 9 reports of seizure not 3. 8 of these seizures occurred in participants who had taken at least one dose of bupropion SR Authors' conclusion: The therapeutic use of bupropion SR at total daily doses up to 300 mg/day in depressed patients without predisposition to seizures is associated with a seizure rate that is well within the range observed with other marketed antidepressants

Study details	Participant characteristics	Results	Comments
Author, Year Johnston 1991[133] **Study design** Uncontrolled cohort study **Intervention details** **Specific intervention** Bupropion 225-450 mg/ day **Comparator** None **Duration of therapy** 8 wks **Duration of follow-up** Unlimited	**Number of participants** n = 3279 **Inclusion/exclusion** Minimum age 18 years; diagnosis of depression for which antidepressant treatment clinically appppropriate Exclude: Previous bupropion use; past or current diagnosis of bulimia or anorexia nervosa; predisposition to seizures; pregnancy, lactation, failure to use an acceptable form of contraceptive (females); had received an MAO inhibitor within the past 14 days or an investigational drug within the past 30 days Patients were not allowed to receive other antidepressants, neuroleptic drugs or amphetamine-type compounds during the study **Baseline characteristics** Sex: 1949/3279 F. Mean (SD) age = 43.5 (13.2) years, Major depression: 2391 Dysthymic disorder: 328 Bi-polar depression: 271 Aypical depression: 190 Atypical bi-polar disorder: 65 Other depressive diagnoses: 34 **Proportion of participants reporting an adverse event** NA	**List of adverse events** 13 grand mal seizures: (4 male, 9 female) 8 during treatment and 5 in the continuation phase 10/13 cases of seizure occurred at a dose of 450 mg/day; 2 at 375 mg/day and 1 at 300 mg/day. 10/13 occurred within 4 hours of the last dose of bupropion, 3/13 within 24 hours. 3/13 seizures occurred within 14 days of starting bupropion therapy, 1/13 between days 15 and 21; 4 between days 29 and 56 and 5 after day 56. 4/13 seizures occurred within one week of a dose change Calculated observed seizure rate during 56 days treatment phase was 0.24% with upper one-sided 95% CI of 0.38%. Observed seizure rate for whole study was 0.40% with upper one-sided 95% CI of 0.58% The survival analysis performd on participants who took 300-450 mg/day (n=2708) showed a cumulative rate of 0.36% in the 56 day treatment period, with upper one-sided 95% CI of 0.57% **Clinical significance** Authors' conclusions: Seizure rates confirm earlier estimates and fall within the accepted parameters for antidepressants **Comments** 84 other adverse events that were life threatening or required hospitalisation were reported: 56 psychiatric, 22 unrelated to drug, 6 possibly bupropion related (drug discontinued). Details vague	

9.7.2.3.2 Bupropion adverse events reported in uncontrolled studies - Cardiovascular events (subjects with co-existing psychiatric disorders)

Study details	Participant characteristics	Results – intervention	Comments
Author, Year Farid 1983 [134] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Bupropion 50 mg tablets (100 mg t.i.d) increasing to 600 mg/day as necessary. (450 mg/day optimal for study) **Comparator** **NA** **Duration of therapy** 14 days, with a min of 7 days at least (450 mg/day) **Duration of follow-up** 14 days, concurrent with treatment	**Number of participants** n = 12 **Inclusion/exclusion** Participants had to have a diagnoisis of depression, to receive no neuroleptic, anxiolytic or other psychoactive drug for at least 1 week prior to the study (longer for certain drugs), and to have a documented history of clinically significant tricyclic-induced orthostatic hypotension within the last 6 months **Baseline characteristics** Participants came from two centers (protocols run separately) Sex: 7/12 M Mean ages: 52 years and 57 years (overall range 36-65) **Proportion of participants reporting an adverse event** NA	**List of adverse events** Variable mean (SD) at placebo baseline; after 14 days bupropion: Supine SBP 126.9 (5.8) mm Hg; 126.0 (6.4) mmHg Supine DBP 79.7 (3.5) mm Hg; 76.3 (4.4) mmHg Standing SBP 120.4 (5.7) mmHg; 116.5 (4.8) mm Hg Standing DBP 80.6 (3.6) mm Hg; 80.2 (4.2) mm Hg Supine minus Standing SBP 6.5 (SD 1.7) mmHg; 9.5 (SD 3.1) mmHg Bupropion produced no significant change in supine or standing SBP or DBP compared with placebo. Fall in SBP upon standing not clinically or statistically significantly different after bupropion than after placebo in these participants who suffered orthostatic hypotension with tricyclics **Comments** Very small sample (n = 12) and many means were calculated with as few as 10 participants. Missing participants are not explained	

Study details	Participant characteristics	Results – intervention	Comments
Author, Year Roose 1991 [135] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Bupropion mean (SD) dose 442 (47) mg/day (b.i.d.) **Comparator** None **Duration of therapy** 3 weeks **Duration of follow-up** 3 weeks, concurrent with treatment	**Number of participants** n = 36 **Inclusion/exclusion** Inpatients with affective disorder needing treatment with antidepressants Patients had CHF, enlarged heart, evidence of bundle branch block, defined as QRS interval greater than 0.10 seconds or more than 10 ventricular premature depolarisations per hour determined by ECg **Baseline characteristics** Mean (SD) age: 69 (9) years Sex: 14/36 M CHF: 15/36 Conduction disorder: 21/36 Ventricular arrhythmias (some with combination): 15/36 **Proportion of participants reporting an adverse event** NA	**List of adverse events** Variables measured at baseline; 3 weeks; statistical difference between treatments: Mean (SD) Pulse rate (bpm): 74.8 (11.9); 76.6 (10.4); NS In participants with impaired LVF (n=15): mean (SD) EF 34% (13); 2% increased (6%) (NS) Pre-existing conduction disease (n=21) Mean (SD) PR interval (secs): 0.162 (0.02); 0.167 (0.03) (p=0.06) Mean (SD) QRS interval 0.126 (0.01); 0.128 (0.02) (NS) Participants with ventricular premature depolarisation. At baseline number recorded: 164 (SD 133); 69 (SD 149) (p=0.12) One participant increased from 56 at baseline to 588 with bupropion, but not necessarily drug related No significant conduction complications and no evidence of a higher degree of AV block during treatment compared to baseline **Comments** In addition to the specific safety issues looked at in this study 5 participants dropped out due to Aes. One participant psoriasis and skin rash, two participants had increase of hypertension, one participant orthostatic hypertension, one participant with history of CAD developed worsening of angina	Discussion of cardiac effects of bupropion.

9.7.2.3.3 Bupropion adverse events reported in uncontrolled studies - Sexual function

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Gardner 1985 [137] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Flexible regimen of bupropion (50 to 600 mg/day) **Comparator** None **Duration of therapy** Up to 1 yr **Duration of follow-up** Unclear	**Number of participants** n = 40 **Inclusion/exclusion** Not reported **Baseline characteristics** Age range: 20 to 60 years (one patient over 60 years, exact age not stated) Major depression: 29/40 participants Bipolar disorder: 11/40 Duration of depression: range, 2 to 20 years. History for sexual dysfunction Negative history: 12 Positive history During antidepressant treatment only: 24 Chronic history: 4 Total positive history: 28 **Proportion of participants reporting an adverse event** NA	**List of adverse events** Of 28/40 participants with sexual dysfunction while on other antidepressants, 24 improved completely over a 1- to 4- month period and experienced no sexual problems (either decreased libido, decreased erectile capacity, or delayed or retrograde ejaculation) whilst receiving bupropion ($p<0.001$). Eighteen were aged 40+ and 10 were <40 yr old All the 10 participants, <40 years improved their sexual functioning while receiving bupropion. The 4 patients who showed no change in their sexual dysfunction ranged in age from 50 to 67. Twelve patients without a history of sexual dysfunction all reported normal sexual functioning **Comments** None	Information supports lack of sexual dysfunction as a common side effect of burpopion

Study details	Participant characteristics	Results	Comments
Author, Year Rowland 1997 [138] **Study design** Uncontrolled study **Intervention details** **Specific intervention** Bupropion 75 mg b.i.d. to 150 mg b.i.d. **Comparator** None **Duration of therapy** 6 weeks **Duration of follow-up** 10 weeks, concurrent with therapy	**Number of participants** n = 15 **Inclusion/exclusion** Diabetic men aged 21 to 60 , with erectile dysfunction (due to diabetes) **Baseline characteristics** Not reported **Proportion of participants reporting an adverse event** NA	**List of adverse events** In this study there was no evidence that bupropion worsened or interferred with sexual desire or erectile functioning. Subjective measures of libido, erectile function, and sexual satisfaction either remained stable or improved mildly during exposure to bupropion. Physiologic measures such as penile bracial index (PBI) and penile sensitivity showed no overall change under bupropion. Autonomic function tests showed a decrease, but this was not statistically significant **Comments** N/A	

9.7.2.3.4 Bupropion adverse events reported in uncontrolled studies - Body weight

Study details	Participant characteristics	Results - intervention	Comments
Author, Year Gardner 1984[136] **Study design** Uncontrolled study	**Number of participants** n = 58 **Inclusion/exclusion** Outpatients diagnosed with a nonpsychotic depressive disorder, who poorly tolerated tricyclic antidepressants (many specifically due to weight gain) **Baseline characteristics** Not reported **Proportion of participants reporting an adverse event** NA	**List of adverse events** After 3, 6, 9 or 12 months on bupropion therapy (mean 9 months) the mean terminal weight change was -4.8 lbs for men and -8.0 lbs for women. Overall 72% lost weight and 24% gained weight, with 4% no changes. Changes in weight corresponded poorly to patients' reports of appetite suppression or increase **Comments** N/A	
Intervention details			
Specific intervention Bupropion 50-600 mg/day (most common 300-450 mg/day) **Comparator** NA **Duration of therapy** Up to one year **Duration of follow-up** Up to one year			

9.7.2.4 Bupropion Adverse events reported in survey-type studies

9.7.2.4.1 Bupropion Adverse events reported in survey-type studies - Sexual Function

<table>
<tr><th>Study details</th><th>Participant characteristics</th><th>Results – Intervention</th><th>Comments</th></tr>
<tr><td>Author, Year
Modell 1997 [139]

Study design
Survey</td><td rowspan="3">Number of participants
Intervention: n = 22
Comparator: fluoxetine, n = 37; paroxetine, n = 21; sertraline, n = 37

Inclusion/exclusion
Psychiatric outpatients taking one of the medications under study for 1 week or more; no reported, symptomatic medical problems or pre-existing sexual dysfunction; taking no other medication commonly associated with or knwn to cause sexual side effects; taking no other psychotrpic medication besides alprazolam or clonazepam

Baseline characteristics
Mean (SD) age: 41 (2.1) years
Sex: 10/22 M
Diagnosis of depression: 22 participants

Proportion of participants reporting an adverse event
Intervention: not reported
Comparator: not reported</td><td>List of adverse events
No reported decreases in sexual function over baseline

Clinical significance
Patients reported significant increases in sexual function over baseline, in terms of libido, arousal, duration and intensity of orgasm

Comments
N/A</td><td rowspan="3">Small study. Attempts made to minimise potential effects of confounding factors and investigator bias</td></tr>
<tr><td>Intervention details</td><td>Results – Comparator</td></tr>
<tr><td>Specific intervention
Bupropion (mean dose 276 mg/day, range 37.5 – 600 mg/day)

Comparator
Mean doses of comparators: fluoxetine 25 mg/day; paroxetine 23 mg/day; or sertraline 110 mg/day.

Duration of therapy
4.8 (SD 1.0) months

Duration of follow-up
NA</td><td>List of adverse events
All control drugs had reported detremental effects on sexual functioning

Comments
Not relevent to smoking cessation therapies</td></tr>
</table>

9.7.2.5 Bupropion adverse events reported in surveillance studies

Study details	Participant characteristics	Results
Author, Year ADRAC 2001 [140] **Study design** Surveillence Data from the Adverse Drug Reactions Advisory Committee, Australia.	**Number of participants** Not reported **Inclusion/exclusion** Not reported **Baseline characteristics** Not reported **Number of participants reporting an adverse event** NA	**List of adverse events** Adverse reaction, No of report Total 780 (758 had bupropion SR as the sole suspected drug) Urticaria, 167; Other rashes, 86; Other itch, 46; Dizziness/ataxia, 78; Headache, 68; Tremor, 57; Convulsions/twitching, 48; Paraesthesia/hypoaesthesia, 40; Insomnia, 78; Agitation, 58; Anxiety, 50; Depression, 45; Nausea, 87; Vomiting, 30; Facial/angioedma, 62; Chest pain, 54; Shortness of breath, 38; Increased sweating, 33; Serum sickness, 33 **Comments** Authors state: ADRAC is satisifed, to date, that bupropion has not emerged as a cause of unexpected deaths
Intervention details		
Specific intervention Bupropion **Comparator** NA **Duration of therapy** NA **Duration of follow-up** NA		

Study details	Participant characteristics	Results
Author, Year Canadian ADR Newsletter 1999 [141] **Study design** Surveillence **Intervention details** **Specific intervention** Bupropion SR use as licenced as Zyban only **Comparator** None **Duration of therapy** Unclear **Duration of follow-up** Aug 18 to Dec 01 1998	**Number of participants** Not stated **Inclusion/exclusion** People trying to stop smoking, use as licenced **Characteristics** Mean age: 36 years (range 27 to 81) **Number of participants reporting an adverse event** There were a total of 48 reports of adverse reactions to bupropion (15 men, 31 women, 2 unknown)	**List of adverse events** The 48 reports included a total of 144 adverse reactions Grouped by body system they were: Central and peripheral nervous system - tremor (6), dizziness (5), hypoesthesia (3), stupor(3), paralysis (2), convulsions grand mal (2), coordination abnormaality (2), hyperkinesia (2), dyskinesia (1), dysaesthesia 91), vertigo (1), speech disorder (1), headache (1), convulsions (1), parasthesia (1) Dermatiological - pruritus (9), urticaria (7), rash (4), rash erythematous (4), erythema multifrome (2), Stevens-Johnson syndrome (1), rash maculo-papular (1); skin discolouration (1); Body - Oedema (7), chest pain (3), face oedema (2), allergic reaction (2), malaise (2), fatigue (2), fever (1), condition agravated (Bells Palsy) (1), aesthenia (1), sensation of wrmth (1), cold extremities (1), oedema peripheral (1), mouth oedema (1), pharynx oedema (1) Psychiatirc - insomnia (5), anxiety (5), suicidal ideation (3), hallucination (3), aggressive reaction (1), anorexia (1), paranoia (1), confusion (1), depression (1), nervousness (1), concentration impaired (1), agitation (1) Cardiovascular - palpitations (2), tachycardia (2), flushing (1), myocardial infarction (1), angina pectoris (1) gastrointestinal - nausea (4), vomiting (3), dysphagia (3), dyspepsia (1) Respiratory - dyspnoea (3), hyperventilation (1), rhinitis (1) Musculoskeletal - arthralgia (1), arthropathy (1), myalgia (1) Opthalmic - vision abmormal (3), mydriasis (1), photophobia (1) Other - earache (1), epistaxis (1) 16 of the reports described serious adverse events, resulting in patients being admitted to hospital or having their hospital stay extended (n=8), death (n=1), convulsions (n=3) or a major medical intervention (n=4) **Comments** N/A

Study details	Participant characteristics	Results
Author, Year MCA 2001 [95] **Study design** Surveillance **Intervention details** **Specific intervention** Bupropion **Comparator** NA **Duration of therapy** NA **Duration of follow-up** NA	**Number of participants** Estimated 390,000 patients **Inclusion/exclusion** Persons treated for smoking cessation as per the UK Product Licence for bupropion SR **Characteristics** Not reported **Number of participants reporting an adverse event** NA	**List of adverse events** Reported reaction, number of reports TOTAL, 5593 (Urticaria, 761; Insomnia, 761; Rashes, 724; Headache, 537; Dizziness, 534; Nausea, 489; Angiodema, 348; Depression, 345; Tremor, 279; Pruritus, 283; Anxiety, 232; Chest pain, 238; Dry mouth, 189; Dysponoea, 184; Palpitations, 174; Agitation, 160; Vomiting, 161; Increased sweating, 145; Chest tightness, 134; Constipation, 133; Arthralgia, 128; Abdominal pain, 119; Seizures, 118 (approximately half of the participants had either a past history of seizures and/or risk factors for their occurrence); Malaise, 118; (sum of reports exceeds total no); Death, 37 (in 9 cases, participants were not taking bupropion at time of death) Estimated incidence of dose-related risk of seizure: 0.1% (1/1000) **Comments** Reactions are not necessarily caused by the drug

9.7.2.6 Bupropion adverse events reported in systematic reviews

REVIEW DETAILS
Author
Holm 2000[13]
Objective: To review the use of bupropion SR in the management of smoking cessation.
Inclusion Criteria
Study design: Any. Prescedent given to large, well controlled trials, with appropriate statistical methodology.
Participants: Using bupropion SR for smoking cessation
Intervention: Bupropion SR
Outcome: Smoking abstinence; adverse events
Exclusion Criteria: Not stated
Quality Assessment: Not stated

RESULTS
Total studies: n = 4
Types of studies: Studies included in systematic review rather vague. For AE data 3 RCTs, 2 prospective safety studies, one retrospective study and several case reports.
Type of smoker: Adults
M/F ratio:
Level of nicotine dependence: Unclear
Fagerstrom score:
Specific intervention:
Comparator:
Specific outcome:
Definition of smoking cessation used:
Duration of follow-up:
Settings:
Participants:
Quality of included studies:

9.8 QUALITY ASSESSMENT OF STUDIES

9.8.1 Quality Assessment of RCTs

NB. Some trials removed for reasons of commercial confidentiality. The results of these individual studies have not been included in the review.

Author, Year	Random allocation?	Method of allocation	Adequate concealment?	No of pts randomised?	Comparable at baseline?	Co-interventions	Inclusion/ Exclusion Criteria	Pts blind?	Assessors blind?	Success of blinding checked	80% followed up	Reasons for withdrawals	ITT analysis
Allen 1995 [58]	Yes	Not stated	Yes	No	Unclear	-	Yes	Yes	Yes	No	Yes	Yes	Unclear
Batey 1998 [123]	Yes	Not stated	Unclear	Yes	Unclear	No	Yes	No	No	No	Unclear	No	Unclear
Braconnier 1983 [120]	Unclear	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Unclear
Clavel-Chapon 1997 [26]	Yes	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	Yes	Yes	Yes
Coleman 1999 [124]	Yes	Not stated.	Yes	Yes	Yes	None reported	Yes	Yes	Yes	No	No	Yes	Yes
Epifano 1992 [61]	Yes	Not stated	Unclear	Yes	Yes	None reported	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear
Fishbein 2000 [54]	Yes	Not stated	No	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
GSK (AK1A4008) 1999 [31]													
GSK AK1406 1999 [516]													
GSK ZYB40003 2001 [50 41]	Yes	Randomised codes	Yes	Yes	Unclear	No	Yes	Yes	Yes	No	No	No	Yes
GSK ZYB40014 2000 [32]													
GSK													

Author, Year	Random allocation?	Method of allocation	Adequate concealment?	No of pts randomised?	Comparable at baseline?	Co-interventions	Inclusion/ Exclusion Criteria	Pts blind?	Assessors blind?	Success of blinding checked	80% followed up	Reasons for withdrawals	ITT analysis
ZYB40017 1999 [42]													
Hardardottir 1996 [118]	Yes	Not stated	Unclear	Yes	Unclear	None stated	Yes	No	Unclear	No	No	Unclear	Unclear
Hertzberg 2001 [51]	Yes	Not stated.	Unclear	Yes	Yes	Yes.	Yes	Yes	Yes	No	Yes	Yes	Unclear
Hurt 1995 [65]	Yes	Not stated	Unclear	Yes	Unclear	None reported	Yes	Unclear	Unclear	No	Yes	Yes	Yes
Jensen 1991 [25]	Yes	Block randomisation	-	No	Yes	No	Yes	No	No	No	Yes	No	Yes
Jordan 1992 [66]	Yes	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Unclear	Unclear
Joseph 1996 [53]	Yes	Computer generated	Yes	Yes	Yes	No	Yes	Yes	Unclear	No	No	Unclear	Yes
Keely 1996 [60]	Yes	Not stated.	Unclear	Yes	Unclear	None reported.	Yes	Unclear	Unclear	No	Yes	Yes	Unclear
Khoury 1996 [62]	Yes	Not stated	Unclear	Yes	Yes	None reported	Yes	Yes	Yes	No	Yes	Yes	Unclear
Kiev 1994 [121]	Yes	Not stated.	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Unclear	Unclear	Unclear
Labbate 2001 [125]	Yes	Not stated.	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	Yes	Yes	No
Lucini 1998 [55]	Yes	Not stated.	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Unclear
Neunteufl 2001 [56]	Yes	Not stated	Unclear	Yes	Unclear	No	No	No	Yes	No	Unclear	N/A	N/A
Nordstrom 1999 [67]	Yes	Not stated	Yes	Yes	Yes	-	Yes	Yes	Unclear	No	Yes	Unclear	Unclear
Oncken 1997 [69]	Yes	Computer generated	Unclear	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No
Roose 1987 [122]	Yes	Not stated	Unclear	Yes	Yes	-	Yes	No	No	No	Yes	Yes	Unclear
Sahba 2000 [59]	Yes	Not stated	Unclear	Yes	Yes	-	Yes	Yes	Unclear	No	Yes	-	-
Sawe 1997 [439]	Yes	Computer generated	Yes	Yes	Yes	None reported	Yes	Yes	Yes	No	No	Yes	Unclear
Segraves 2000 [126]	Yes	Not stated	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	incomplete	No
Settle 1999 [445]	Unclear	Not stated	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear
Solomon 2000 [28]	Yes	Not stated	Unclear	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes

Author, Year	Random allocation?	Method of allocation	Adequate concealment?	No of pts randomised?	Comparable at baseline?	Co-interventions	Inclusion/ Exclusion Criteria	Pts blind?	Assessors blind?	Success of blinding checked	80% followed up	Reasons for withdrawals	ITT analysis
Study 2000 [30]	Yes	Computer-generated/Block randomisation	Yes	Yes	Yes	Not stated	Yes	Yes	Yes	No	No	Yes	Yes
Tashkin 2001 [45]	Yes	Block randomisation	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	No	Yes	Yes
Tzivoni 1996 [64]	Yes	Not stated	Yes	Yes	Unclear	None reported	Unclear	Yes	Yes	No	Unclear	No	Unclear
Tzivoni 1998 [115]	Unclear	Not stated	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes
West 2000 [68]	Yes	Not stated	Unclear	Yes	Unclear	-	Yes	No	No	No	Unclear	Unclear	
Wisborg 2000 [29]	Yes	Randomisation list and code	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wong 1999 [27]	Yes	Computer generated.	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes
Working group 1994 [57]	Yes	Block randomisation	Yes	Yes	Yes	-	Yes	Yes	Yes	No	Yes	Unclear	Yes

9.8.2 Quality assessment of non-randomised controlled studies

Author, Year	Random allocation?	Method of allocation	Adequate concealment?	No of pts recruited	le at baseline?	Co-interventions	Inclusion/ Exclusion Criteria	Pts blind?	Assessors blind?	of blinding checked	80% followed up	Reasons for withdrawals	ITT analysis
Benowitz 1993 [72]	No	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	Yes	Unclear	Unclear
Netscher 1995 [70]	No	Crossover study	No	No	Yes	None stated	Yes	No	No	No	Yes	Unclear	Unclear
Wenger 1983 [127]	No	Unclear	Unclear	No	Unclear	None stated	No	Yes	Yes	No	Unclear	Unclear	Unclear
Zevin 1998 [71]	No	Crossover study	No	Yes	Yes	None stated	Yes	No	No	No		None	Yes

9.8.3 Quality assessment of uncontrolled studies

Author, Year	Group clearly stated?	Control group?	If no control - okay?	Follow-up adequate?	Aims?	Study design appropriate ?	Sample size appropriate ?	Valid measurements?	Valid outcome measurements	All pts accounted for?	Are statistics well described?	appropriate ?
Bende 1998 [76]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	NA	NA
Bircher 1991 [82]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	NA	NA
Bjornson-Benson 1993 [77]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA
Davidson 1989 [131]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Dunner 1998 [132]	Yes	No	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Farid 1983 [134]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	No	Yes
Fredrickson 1995 [73]	Yes	No	No	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes
Gardner 1984 [136]	Yes	No	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Gardner 1985 [137]	Yes	No	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear
Girdler 1997 [297]	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Gourlay 1999 [74]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear
Hatsukami 1993 [80]	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Unclear	Unclear

Author, Year	Group clearly stated?	Control group?	If no control - okay?	Follow-up adequate?	Aims?	Study design appropriate ?	Sample size appropriate ?	Valid measurements?	Valid outcome measurements	All pts accounted for?	Are statistics well described?	Statistics appropriate ?
House 1995 [78]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	NA	NA
Hurt 1998 [75]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Johnston 1991 [133]	Yes	No	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Unclear
Krivokapich 1984 [63]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Mahmarian 1997 [86]	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Martin 1996 [377]	Yes	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Unclear	No	Yes
McNabb 1984[79]	Yes	Yes	NA	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	NA	NA
Mills 1997[83]	Yes	No	Unclear	No	Unclear	Unclear	No	Unclear	Unclear	Yes	NA	NA
Moffat 2000 [88]	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Nitenberg 1999[87]	Yes	No	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Ogburn 1999[90]	Yes	No	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Roose 1991 [135]	Yes	No	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	Unclear

Author, Year	Group clearly stated?	Control group?	If no control - okay?	Follow-up adequate?	Aims?	Study design appropriate ?	Sample size appropriate ?	Valid measurements?	Valid outcome measurements	All pts accounted for?	Are statistics well described?	Statistics appropriate ?
Roth 1999 [129]	Yes	No	Unclear	No	Yes	No	No	Unclear	Yes	Unclear		
Rowland 1997 [138]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear
Sarabi 2000 [84]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Schuh 1997 [89]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Stein 1996 [85]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
van Wyck Fleet 1983 [130]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Wallstrom 1999 [81]	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Zevin 1998 [71]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	NA	NA

9.8.4 Quality assessment of case control studies

Author, Year	Kimmel, 2001 [92]
Was the method used to obtain cases appropriate?	Yes
Were controls selected appropriately?	Yes
Were data collected in the same way for cases and controls?	Yes
Was follow-up adequate?	Yes
Aims clearly stated?	Yes
	Yes
Sample size appropriate?	Unclear
Measurements valid and reliable?	Yes

Were the outcome measures appropriate?	Yes
All participants accounted for?	Yes
Were all the statistical methods well described?	Yes
Were the statistical methods appropriate?	Yes
Was there data dredging?	No
Was there risk of significant bias?	Unclear

9.8.5 Quality assessment of survey-type studies

Author, Year	Aims clearly stated?	Population studies appropriate?	Statistical methods well described?	Statistical methods appropriate?	Was there risk of significant bias?
Modell, 1997 [139]	Yes	Yes	Yes	Yes	Unclear

9.8.6 Quality assessment of surveillance studies

Author, Year	Source of data clearly stated?	Is the population appropriate?	Any specific data not included?	Are any statistics performed on the database appropriate?	Are the statistics well described?	Are the statistics methods appropriate?
ADRAC, 2001 [140]	Yes	Yes	No	Yes	N/A	N/A
Canadian ADR newsletter, 1999 [141]	Yes	Yes	No	N/A	N/A	N/A
MCA, 2001 [95]	Yes	Yes	No	Yes	N/A	N/A
Ottervanger, 1997 [94]	Yes	Yes	Unclear	N/A	N/A	N/A
Preskorn, 1995 [411]	Unclear	Unclear	No	N/A	N/A	N/A
Spiller, 1994 [461]	Yes	Unclear	Yes	Yes	Yes	Yes
Spyker, 1996 [93]	Yes	Yes	Unclear	Unclear	No	Unclear
Spyker, 1998 [117]	Yes	Yes	Unclear	Yes	Unclear	Unclear

9.8.7 Quality assessment of systematic reviews

Author, Year	Fiore, 2000[23]	Greenland, 1998[52]	Holm 2000[13]	Hughes, 2000[40]	Silagy, 2001[24]
Inclusion/exclusion criteria relate to study design of interest?	✓	✓	✓	✓	✓
Inclusion/exclusion criteria relate to participants of interest?	✓	✓	✓	✓	✓
Inclusion/exclusion criteria relate to intervention of interest?	✓	✓	✓	✓	✓
Inclusion/exclusion criteria relate to outcomes of interest?	✓	✓	✓	✓	✓
Inclusion/exclusion criteria applied by more than one author?	✓	x	x	x	✓
Valid inclusion exclusion criteria	✓	✓	✓	✓	✓
Validity systematically assessed	x	x	x	✓	✓
Validity criteria applied by more than one author?	x	x	x	X	✓
Validity taken into account in synthesis?	x	x	x	x	X
Data extraction performed by more than one author?	✓	x	x	✓	✓
Are primary studies presented in sufficient detail?	x	✓	✓	✓	✓
Have the primary studies been synthesised appropriately?	✓	✓	✓	✓	✓
Has a meta-analysis been performed?	✓	✓	x	✓	✓
If Yes, has heterogeneity been formally assessed?	✓	✓	x	✓	✓

9.9 CASE REPORTS AND CASE SERIES INCLUDED IN THE REVIEW

9.9.1 NRT CASE REPORTS AND CASE SERIES

Author, Year	Intervention details	Patient characteristics	Adverse event(s)
Brandspigel 1987[98]	Nicotine gum **Concomitant medication** None reported	32-year-old male diagnosed with a duodenal ulcer	Severe vomiting
Dousset 1986[99]	Nicotine gum (20 mg nicotine) **Concomitant medication** None reported	29-year-old male	Increase in serum triglycerides and cholesterol.
Einarson 1997[100]	Nicotine gum (Nicorette 2 mg) **Concomitant medication** Hydrochlorothiazide/triamterene	51-year-old female smoker (8 cigarettes/day)	Abrupt, forceful hiccups, 15 minutes in duration.
Farm 1993[101]	Nicotine patch (14 mg/24 h) and nicotine gum **Concomitant medication** None reported	54-year-old female	Red, swollen itchy skin under the patch area. After discontinuation of the patch, the skin reaction worsened and similar reactions appeared at previous patch sites. Whilst using the nicotine gum, symptoms worsened.
Foulds 1995[102]	Nicotine patch (Nicorette 15 mg) **Concomitant medication** None reported	43-year-old female smoker (20-30 cigarettes/day). The patient was involved in a study which involved 1 week of smoking at will whilst wearing the patch.	Suspected nicotine intoxication. Patient awoke feeling dizzy, nauseous and weak. Suffered delusions and hallucinations.
Frazier 1993[103]	Nicotine patch (ProStep 14 mg) **Concomitant medication** None reported	31-year-old female	Swelling of feet, legs, hands, face and throat and a blisterlike rash under the adhesive.
Goodman 1987[104]	Nicotine gum **Concomitant medication** Hydrocholrothiazide and levothyroxine	37-year-old female with mild hypertension, hay fever and hyperthyroidism.	Rash appeared in the mouth 15-20 minutes after chewing a piece of gum. The rash completely disappeared when the patient stopped chewing the gum.
Jackson 1993[105]	Nicotine patch (30 mg, Nicotinell TTS 30) **Concomitant medication** None reported	62-year-old female	After three weeks of using the patch, the patient suffered severe throbbing headache and nausea. After stopping using the patch, the patient experienced four further migraine-like headaches. Diagnosed with reversible widespread segmental cerebral arterial narrowing.
Lavuad 1994[106]	Nicotine patch (Nicopatch 30 cmxcm) **Concomitant medication** None reported	47-year-old male	Patient was stung on patch site by a wasp. Developed an anaphylactoid reaction.

Author, Year	Intervention details	Patient characteristics	Adverse event(s)
Moreau 1997[107]	Nicotine patch (Nicotinell 21 mg/24h) **Concomitant medication** None reported	48-year-old male smoker (40 cigarettes/day) suffering from myasthenia gravis.	Symptoms of myasthenia gravis became more severe.
Ottervanger 1995[108]	Nicotine patch (Nicotinell 21 mg) **Concomitant medication** None reported	39-year-old male smoker (50-100 cigarettes/day) who 2 years previously had suffered from chest pain following an accident.	Severe chest pain with sweating and nausea. Patient was diagnosed with a myocardial infarction.
Pierce 1994[109]	Nicotine patch (10 mg) **Concomitant medication** Cimetidine and dexamethasone	40-year-old male with spasm of the right middle cerebral artery and an aneurysm of the right internal carotid artery.	Patient suffered a stroke after application of the nicotine patch.
Sick 1993[110]	Nicotine patch, 30 mg **Concomitant medication** None reported	33-year-old male smoker (30 cigarettes/day)	Tachyarrythmia, loss of consiousness and agitation upon application of the patch.
Stewart 1985[111]	Nicotine gum (Nicorette 2 mg), 20-30 pieces/day **Concomitant medication** None reported	35-year-old healthy male	Patient developed atrial fibrillation (150 beats/min).
Vincenzi 1993[112]	Nicotine patch (Nicotrans 30 mg) **Concomitant medication** None reported	***Case 1***. 46-year-old female with history of eczema. ***Case 2***. 40-year-old female ***Case 3.*** 46-year-old female with chronic dermatitis	***Case 1.*** Patient experienced pruritus and erythematovesicular patches appeared on all patch application sites. ***Case 2.*** Patient developed a pruritic erythematovesicular eruption at patch application sites. ***Case 3.*** Itching and erythema occurred at all patch application sites. Also experienced an intense buring sesation.
von Bahr 1997[113]	Nicotine patch **Concomitant medication** None reported	46-year-old female, heavy smoker.	Itch and erythema appeared, persisting for several days.
Warner 1994[114]	Nicotine patch, 21 mg **Concomitant medication** None reported	47-year-old male smoker who had previously suffered an inferior myocardial infarction.	Patient smoked whilst continuing to wear the patch and developed severe chest pain. Diagnosed with a myocardial infarction.

9.9.2 BUPROPION CASE REPORTS AND CASE SERIES

Author, Year	Intervention details	Patient characteristics	Adverse event(s)
Amann 2000 [143]	Bupropion SR 300 mg/d **Concomitant medication** Lamotrigine and olanzapine	38-year-old female diagnosed with schzioaffective disorder.	Hypesthesia of two branches of the left tringeminal nerve. Perception of touch and pain appeared impaired.

Ames 1992 [144]	***Case 1.*** Bupropion 150 mg b.i.d. ***Case 2.*** Bupropion 300 mg/d. ***Case 3.*** Bupropion 75 mg b.i.d. **Concomitant medication** ***Case 1.*** Lithium carbonate, clonazepam, propanolol, and temezapam. ***Case 2.*** Lithium carbonate and cimetidine. ***Case 3.*** None reported	***Case 1.*** 63 year old male with anergic nonpsychotic depression ***Case 2.*** 50 year old male with a history of bipolar illness ***Case 3.*** 23 year old female with a history of intermittant atypical depressive episodes.	***Case 1.*** Visual hallucinations. ***Case 2.*** Feelings of paranoia, and visual and aural hallucinations. Patient experienced a subjective sense of disorientation and confusion. ***Case 3.*** Night-time visual hallucinations.
Balon 1996 [145]	Bupropion 150 mg/d **Concomitant medication** Conjugated oestrogen.	55 year old white female who suffered from bipolar II disorder.	Suffered from nightmares, and experienced 'cold sweats and anxiety and anger upon awakening'.
Bittman 1991[146]	Bupropion 75 mg/d **Concomitant medication** Diltiazem	78-year-old male with history of recurrent major depression.	Patient developed mania.
Dager 1990 [147]	Bupropion 375 mg/d **Concomitant medication** Lithium carbonate and propanolol	48-year-old male with a history of bipolar illness	Patient suffered from delerium.
David 1999[148]	Bupropion 150 mg b.i.d **Concomitant medication** glipizide and metformin	49-year-old male with posttraumatic stress disorder and type II diabetes.	Patient was found to suffering from rhabdomyolysis associated with hepatic dysfunction.
Fichtner 1992[149]	Bupropion 100 mg t.i.d **Concomitant medication** Lithium carbonate	50-year-old HIV positive male with history of depression.	Patient attempted suicide and then 2 weeks later 'cycled upward into a manic state'.
Gardos 1997 [150]	Bupropion 225 mg/d **Concomitant medication** Lithium carbonate, nicardipine and levothyroxine.	70-year-old female with a history of bipolar disorder.	Patient developed dyskinesia characterised by frequent eye blinking, moderately severe blepharospasm and curling tongue movements.
Golden 1985 [151]	***Case 1.*** Bupropion 500 mg/d. ***Case 2.*** Bupropion 300 mg/d. ***Case 3.*** Bupropion 425 mg/d. ***Case 4.*** Bupropion 100 mg/d **Concomitant medication** ***Case 1, 3 & 4.*** None reported. ***Case 2.*** Lithium carbonate, L-thyroxine and furosemide	***Case 1.*** 35-year-old female suffering from depression. ***Case 2.*** 75-year-old female with history of rapid cycling manic-depressive illness. ***Case 3.*** 54-year-old female with history of manic-depressive illness (non-psychotic). ***Case 4.*** 50-year-old female with history of bipolar II disorder	***Case 1.*** Patient became acutely psychotic. ***Case 2.*** Patient experienced visual and auditory hallucinations. ***Case 3.*** Patient 'suddenly' became psychotic, with marked agitation. ***Case 4.*** Patient developed visual hallucinations.
Goren 2000 [152]	Bupropion 600 mg/d **Concomitant medication** gabapentin	44-year-old male suffering from bipolar affective disorder	Patient experienced a manic episode.
Halbreich 1991 [153]	***Case 1.*** Bupropion 450 mg/d. ***Case 2.*** Bupropion 450 mg/d **Concomitant medication** None reported	***Case 1.*** 30-year-old female with history of major depressive disorder (MDD) (melancholic type), postpartum depression and migraine headaches. ***Case 2.*** 28-year-old female with diagnosis of MDD (melancholic type).	***Case 1.*** Shortened menstrual cycle marked by heavy, prolonged menstrual bleeding ***Case 2.*** Shortened menstrual cycle and irregularites

Howard 1999 [154]	Bupropion 100 mg t.i.d **Concomitant medication** Ibuprofen, sucralfate, colchicine and betaxolol hydrochloride opthalmic solution.	79-year-old male diagnosed with an initial episode of severe major depression following a suicide attempt.	Paranoia and auditory hallucinations.
Hu 2000[155]	Bupropion 200 mg/d **Concomitant medication** None	41-year-old male with history of chronic hepatitis C and major depression.	Acute hepatitis.
Humma 1999 [156]	Bupropion 100 mg t.i.d **Concomitant medication** Captopril, metoprolol, furosemide, cimetidine, diltiazem, asprin, nitroglycerin patch, simvastin and beclomethasone, albuterol and ipratropium inhalers.	67-year-old male smoker with a positive history for myocardial infarction, coronary artery bypass surgery, ischaemic stroke, hypertension, hyperlipidemia, peptic ulcer disease, and chronic obstructive pulmonary disease.	Diagnosed with presumptive transient ischaemic attacks.
Jackson 1992 [157]	Bupropion 75 mg t.i.d **Concomitant medication** None reported	19-year-old male suffering from depression.	Catatonia. Patient became withdrawn and unresponsive.
Kanani 2000 [158] **(Abstract)**	Bupropion SR (dose not reported) **Concomitant medication** None reported	Not reported	Four cases of serum sickness-like reaction.
Labbate 1998 [159]	Bupropion SR 150 mg t.i.d **Concomitant medication** None reported	37-year-old male with history of atttention-deficit disorder	Increased libido and spontaneuous erections.
Levenson 1995 [160]	Bupropion 100 mg b.i.d **Concomitant medication** None reported.	50-year-old female with major depression and irritable sydrome.	Clitoral priapism and prolonged sexual arousal. Discontinuation of bupropion resulted in the spontaneous resolvement of the priapism and arousal.
Liberzon 1990 [161]	Bupropion 75 mg b.i.d **Concomitant medication** Haloperidol, amantadine, and benztropine.	75-year-old male with idiopathic parkinsonism	Patient became disorientated and agitated, with visual and auditory hallucinations, impaired attention and memory, and a fluctuating level of awareness.
Mainie 2001 [162]	OVERDOSE Bupropion 3.75g **Concomitant medication** None	19-year-old healthy female	Two brief generalised seizures. Was discharged from hospital the next day.
Malesker 1995 [163]	Bupropion 100 mg b.i.d **Concomitant medication** glyburide and tolmetin.	72-year-old female with medical history of coronary heart disease, adult-onset diabetes, hypertension, and chronic limb pain.	Eosinophilia diagnosed upon examination. Absolute eosinophil count returned to normal upon discontinuation of all drugs.
Masand 1993 [164]	Intervention Bupropion up to 350 mg/d **Concomitant medication** Phenazine	36-year-old female with short history of depression (with psychotic features).	Patient devloped a manic syndrome.

McCollum 2000 [165]	Bupropion (no dose not reported) **Concomitant medication** ***Case 1 and 2.*** None reported. ***Case 3.*** Clonazepam, acetaminophen with codeine, valproic acid and diphenhydramine.	***Case 1.*** 27-year-old female. ***Case 2.*** 46-year-old male ***Case 3.*** 43-year-old female with a history of bipolar affective disorder	***Case 1.*** Drug reaction to bupropion, charactersied by a pruritic skin rash. ***Case 2.*** Presumed allergic reaction to bupropion. ***Case 3.*** Pruritic rash and arthalgias.
Patten 1999 [167]	***Case 1.*** Bupropion 150 mg/d ***Cases 2 to 5***. Bupropion 300 mg/d for 7 weeks, then bupropion or placebo **Concomitant medication** None reported	***Case 1.*** 45-year-old female smoker (25 cigs/d) with a history of 1 major depressive episode ***Case 2.*** 54-year-old female smoker (20 cigs/d) had previously suffered 1 major depressive episode ***Case 3.*** 35-year-old female smoker (20 cigs/d) ***Case 4.*** 55-year-old female smoker (30 cigs/d), history of 2 previous episodes of depression ***Case 5.*** 44-year-old male smoker (20 cigs/d) had previously suffered 1 major depressive episode	***Case 1.*** Developed moderate major depressive symptoms ***Case 2.*** Diagnosed with major depression. Patient reported 'increased stress due to family problems' and was found to be on placebo. ***Case 3.*** Patient reported irritabilty and 'the jitters' and was diagnosed with dysthymic disorder. Assigned to placebo. ***Case 4.*** Developed marked depressive symptoms, diagnosed with major depression. ***Case 5.*** Diagnosed with major depression. Assigned to placebo.
Patti 1998 [166]	OVERDOSE Bupropion 9 g **Concomitant medication** None reported	32-year-old healthy male	Patient was agitated and tremulous and developed a grand mal seizure.
Peloso 1999 [168]	Bupropion 300 mg/d **Concomitant medication** None reported	21-year-old male	Allergic reaction to buprorpion, characterised by diffuse achiness of the shoulders and hips on day 10, and on subsequent days diffuse swelling of the fingers, toes, knees and eylids.
Ramasubbu 2000[169]	Bupropion SR 300 mg/d **Concomitant medication** Lithium carbonate, paroxetine, trytophan and zopiclone	38-year-old female with history of bipolar II disorder and alcohol abuse	Decreased sexual arousal and lubrication, and delayed orgasm.
Settle 1991 [170]	***Case 1.*** Bupropion 450 mg/d. ***Case 2.*** Bupropion 100 mg t.i.d. **Concomitant medication** None reported.	***Case 1.*** 50-year-old female with a history of recurrent major depressive episodes. ***Case 2.*** 52-year-old female with a history of depressive symptoms.	Both patients experienced a subacute onset of bilateral tinnitus.
Sheehan 1986 [171]	Bupropion 600 mg/d **Concomitant medication** None reported.	25-year-old female with history of chronic anxiety accompanied by panic attacks and phobias.	generalised convulsion with tonic and clonic phases, loss of consiousness and postictal confusion.
Szuba 1992 [172]	***Case 1.*** Bupropion 400 mg/d. ***Case 2.*** Bupropion 450 mg/d **Concomitant medication** None reported.	***Case 1.*** 85-year-old female with multi-infarct dementia. ***Case 2.*** 72-year-old female with a history of bipolar disease	***Case 1.*** gait unsteadiness which upon discontinuation of bupropion resolved itself over 2 weeks. ***Case 2.*** Patient developed a shuffling, magnetic gait.
Tripathi 1999 [173]	Bupropion 300 mg/d **Concomitant medication** None reported	44-year-old healthy female	Serum sickness-like reation. Patient developed arthralgias, myalgias, fatigue, and fevers and chills.

van Putten 1990 [174]	Bupropion 300 mg/d **Concomitant medication** Fluoxetine	41-year-old male suffering from non-psychotic anergic depression.	Patient developed 'myoclonic jerking' and became severely agitated and psychotic.	
Workman 1992 [175]	Bupropion 100 mg t.i.d **Concomitant medication** None reported	44-year-old male with history of major depression and chronic pain.	Patient exhibited a 12-lb weight gain and reported carbohydrate craving. After 8 weeks of treatment the patient had gained 31-lbs.	
Yolles 1999 [176]	Bupropion SR, 150 mg/d **Concomitant medication** Olanzapine, lithium carbonate, and levothyroxine	45-year-old male diagnosed with recurrent depression with psychotic features and schizoaffective disorder (depressed type).	Drug hypersensitivity reaction. Five days after the introduction of bupropion the patient developed a high temperature, joint and chest pain, and a rash.	
Zubieta 1991 [177]	Bupropion 200 mg/d. **Concomitant medication** Lithium carbonate	33-year-old (sex not reported) with a history of hypomania and mania precipitated by maprotiline and phenelzine, and two prior psychiatric hospitalisations secondary to severe depression.	Patient experienced marked increase in anxiety symptoms, progressing to a manic episode.	

9.10 ECONOMIC DATA EXTRACTION TABLES

STUDY (YEAR) - COUNTRY - PARTICIPANTS	INTERVENTIONS AND ESTIMATED CESSATION RATES, AND METHODS	METHODS FOR ESTIMATING LYS OR QALYS, AND ADJUSTING FACTOR	CATEGORIES OF COSTS CONSIDERED	- VIEW POINTS - DISCOUNT RATE - DEALING WITH UNCERTAINTY	RESULTS	AUTHORS' CONLUSIONS. COMMENTARY
Parrott et al (1998) [22] - UK - Participants: A health authority with the national average population of 500,000 and national smoking rates.	- Brief advice: 3% - Advice +self help material: 4% - Above +NRT: 6% - Above +Specialist service: 10% without NRT or 20% with NRT. Spontaneous quit rate: 1%. Relapse rate: 0% (Based on systematic reviews)	PREVENT model LYS/quitter: 0.99	GP time; training; self-help materials; costs of NRT, smokers' clinics. Patients' time and travel.	- View points: NHS and society. - Discount rate: cost: not discounted health benefits: 1.5% . - Sensitivity analysis limited to comparing results with or without discounting.	(UK£, 1997) Brief advice: £174/LYS; £172/quitter. Above + self help material: £221/LYS; £218/quitter. Above + NRT: £269/LYS; £267/quitter. Special clinics + NRT: £255/LYS; £252/quitter. (Reference: current practice)	Smoking cessation remains better value than many life preserving medical intervention.
Orme et al (2001) [184] - UK - Participants: A cohort of UK smoker.	- Pharmacological treatment: 13% - GP advice: 3% - Group therapy: 9% No intervention: 1% Relapse rate: 30%. (Based on literature reviews)	HECOS model LYS/quitter: 0.4	Only total cost presented. The model can also estimate long-term medical expenditure due to smoking related diseases.	- View points: NHS and society. - Discount rate: long-term costs 6%; health benefits 0%. - Sensitivity analysis.	(UK£, 1999) Pharmacological therapy: £649/quitter GP advice: £92/quitter Group therapy: £1148/quitter Average: £1212/LYS. (Reference: willpower)	This model successfully captures the complexity required to model smoking behaviour and associated mortality, morbidity and health care costs. Reviewers' comments: The model is easy to use.
Akehurst (1994) - UK - Participants: Smokers aged 20 or above; males and females, heavy, medium and light smokers in appropriate proportion.	- GP advice: 3.7% - GP advice +NRT patches: 11.7% Spontaneous quit rate: 1%. Relapse rate: 0% (Based on results of individual trials)	PREVENT model LYS/quitter: 0.49 (13.1/27) , or 0.33 (35.2/107), or 0.28 (22.12/80).	GP time; costs of NRT.	- View points: the UK NHS. - Discount rate: costs: not discounted health benefit 6%. - No sensitivity analysis.	(UK£, 1992) GP advice +NRT patch: £4526/LYS; £1252/quitter. (Reference: GP advice alone)	The use of nicotine patches in addition to GP counselling represents good value for money in comparison with other accepted health interventions.

STUDY (YEAR) **- COUNTRY** **- PARTICIPANTS**	**INTERVENTIONS AND ESTIMATED CESSATION RATES, AND METHODS**	**METHODS FOR ESTIMATING LYS OR QALYS, AND ADJUSTING FACTOR**	**CATEGORIES OF COSTS CONSIDERED**	**- VIEW POINTS** **- DISCOUNT RATE** **- DEALING WITH UNCERTAINTY**	**RESULTS**	**AUTHORS' CONLUSIONS.** **COMMENTARY**
Akehurst (1994a) - UK - Participants: Heavy smokers (>23 cigarettes per day).	- GP counselling: 3.7%. - Couns+NRT nasal spray: 26.0% (16% used in sensitivity analysis). Spontaneous quit rate: 1%. Relapse rate: 0%. (Based on results of a RCT)	PREVENT model LYS/quitter: 0.5 (6% discount rate) 2.0 (0% discount rate)	GP time and costs of NRT. Also estimated treatment costs saved.	- Viewpoints: the UK NHS. - Discount rate: costs: not discounted health benefit 6%. - Sensitivity analysis.	(UK£, 1993) NRT nasal spray: £765/quitter £19,160/death avoided £1527/LYS (Reference: GP counselling only)	Cost per life year saved by a programme of counselling plus use of Nicorette nasal spray in heavy smokers compares favourably with other NHS interventions at around £1430 per life year saved.
Stapleton (1999) [185] - UK - Participants: Dependent smokers (>14/day) who were motivated to stop.	- GP counselling: 4.5% (2.8-6.2%). - GP advice +NRT patch (*ACT model): 9.6% (7.9-11.3%). Spontaneous quit rate: 1.5% (1.2-1.8%). Relapse rate: 40% (30-50%). (Based on authors' own RCT)	According to Doll et al's study of a cohort of male gPs. LYS/quitter <35 yr: 1.69; 35-44 yr: 1.94; 45-54 yr: 1.55; 55-65 yr: 1.08. (Note: no. of quitters without relapse)	GP or nurse time; costs of NRT; booklets; biochemical validation.	- Viewpoints: the payers. - Discount rate: costs: not discounted health benefits: 1.75 (1.4-2.1%). - Sensitivity analysis	(UK£, 1998) GP advice + NRT patch: £670 ~ £845/quitter. <35 yr old, £398/LYS; 35-44 yr old, £345/LYS; 45-54 yr old, £432/LYS; 55-65 yr old, £785/LYS. (Reference: GP advice only)	The low cost per life year saved would make GP intervention against smoking a cost-effective life-saving treatment. Commentary: 1. ACT - abstinence contingent treatment. 2. used data from a trial and a survey of associated resource use in 30 gPs.
Crealey (1998) [183] - UK - Participants: Smokers who visit community pharmacies in Northern Ireland.	- The Pharmacist Action on Smoking (PAS) programme: 10% (5-25%). Spontaneous quit rate: 1%. Relapse rate: 10% (0-15%). (Based on results of a pilot study)	More details in Table III. Based on life expectancies of smokers vs non-smokers in the US. LYS/quitter: Age Men Women 35-44, 1.5 0.7 45-54, 2.0 1.1 55- , 2.4 2.1	PAS materials; pharmacists training and time; (excl costs of NRTs which were from smokers' pockets).	- View points: The NHS. - Discount rate: costs: not discounted health benefits, 4%. - Sensitivity analysis.	(UK£, 1997) PAS programme: £509/quitter. (Depending on age groups) men, £197-351/LYS; women, £181-772/LYS. (Reference: no PAS prog.)	PAS service model could be more cost-effective than a number of other accepted disease prevention practices. Even pessimistic baseline assumptions result in favourable cost-effectiveness.

STUDY (YEAR) - COUNTRY - PARTICIPANTS	INTERVENTIONS AND ESTIMATED CESSATION RATES, AND METHODS	METHODS FOR ESTIMATING LYS OR QALYS, AND ADJUSTING FACTOR	CATEGORIES OF COSTS CONSIDERED	- VIEW POINTS - DISCOUNT RATE - DEALING WITH UNCERTAINTY	RESULTS	AUTHORS' CONLUSIONS. COMMENTARY
Cromwell (1997) [186] - US - Population: Adult smokers (>18 yr old) in the US.	- Minimal counselling: alone, +NRTptch, +NRTgum 5.9%, 11.7%, 8.7% - Brief counselling: alone, +NRTptch, +NRTgum 6.9%, 13.4%, 10.0% - Full counselling: alone, +NRTptch, +NRTgum 11.2%, 21.0%, 15.9% - Intensive counselling alone, +NRTptch, +NRTgum 11.6%, 21.6%, 16.5% Spontaneous quit rate: 5% (included in rates above). Relapse rate: 45%. (Based on a meta-analysis for the AHCPR guideline)	According to the methods used in Fiscella & Franks (1996). LYS/quitter: 1.46. QALYS/quitter: 1.97. (Note: no. of quitters after relapse)	Costs of physicians for screening, advising and motivating; direct costs of interventions (educational materials, NRTs).	- Viewpoints: the payers. - Discount rate: costs: not discounted health benefits: 3%. - Sensitivity analysis.	(US$, 1995) (From intensive to minimal) Counselling without NRT $2186 - 7922/quitter; $1496 - 5423/LYS; $1108 - 4015/QALYS. Counselling + NRTpatch $2310 - 4745/quitter; $1581 - 3248/LYS; $1171 - 2405/QALYS. Counselling + NRTgum $3596 - 8962/quitter; $2461 - 6135/LYS; $1822 - 4542/QALYS. (Reference: no intervention)	Compared with other preventive interventions, smoking cessation is extremely cost-effective. The more intensive the intervention, the lower the cost per QALY saved, which suggests that greater spending on interventions yields more net benefits.
Fiscella (1996) [187] - US - Participants: Adult smokers (25-69 yr old). A base case involving a 45 yr old male smoker.	- Physician counselling: 4.0%. - Counselling +NRT ptch: 7.9% (based on OR of 2.06 applied to spontaneous quit rate) Spontaneous quit rate: 2.5%. Relapse rate: 35%. (Based on meta-analysis)	According to mortality data from various sources QALYS/quitter: 1.98 (0.69 ~ 2.38) (Note: no. of quitters after relapse)	Physician time, and retail price of NRT patch.	- Viewpoints: the payer. - Discount rate: costs: not discounted health benefits: 3%. - Sensitivity analysis and Monte Carlo simulation.	(US$, 1995) Counselling + NRTpatch $7332/quitter (lifetime) Costs/QALYS: Age men women 25-44, $4546, $5522 45-54, $5011, $5041 55-64, $7189, $5672 65-69, $10943, $6983 (Reference: counselling alone)	Use of NRT patch among men and women in primary care is relatively cost-effective.

STUDY (YEAR) - COUNTRY - PARTICIPANTS	INTERVENTIONS AND ESTIMATED CESSATION RATES, AND METHODS	METHODS FOR ESTIMATING LYS OR QALYS, AND ADJUSTING FACTOR	CATEGORIES OF COSTS CONSIDERED	- VIEW POINTS - DISCOUNT RATE - DEALING WITH UNCERTAINTY	RESULTS	AUTHORS' CONLUSIONS. COMMENTARY
Oster et al (1986) [188] - US - Participants: A hypothetical group of 250 smokers seen during routine office visits.	- Physicians' advice: 4.5% - Advice + NRT gum: 6.1% Spontaneous quit rate: 1% Relapse rate: 0% (Based on meta-analysis)	According to data from the Am Cancer Soc 25 state Cancer Prev Study. LYS/quitter: Age, men women 35-44, 1.03, 0.57 45-54, 1.09, 0.64 55-69, 0.82, 0.55	Physician time, cost of NRT gum.	- Viewpoints: the payers. - Discount rate: cost: not discounted health benefits: 5% - Sensitivity analysis.	(US$, 1984) Advice + NRT gum $3027/quitter Costs/LYS: Age men women 35-44, $4526, $8421 45-54, $4140, $7034 55-69, $5395, $8129 (Reference: advice alone)	Nicotine gum is a cost-effective adjunct to physician's advice against cigarette smoking in a primary care setting.
Wasley et al (1997) [189] - US - Participants: A hypothetical group of 400 smokers (>20 cigarettes/day), aged 35-69 yr. A base case involving a 45 yr male smoker.	- Physician's advice: 4.5% - Advice + NRT patch: 17.6% Spontaneous quit rate: 1% Relapse rate: 35% (Based on meta-analysis)	Using data and methods in Oster et al (1986). LYS/quitter: See Oster et al (1986)	Physician time, NRT patch prescription.	- Viewpoints: payers. - Discount rate: cost: not discounted health benefits: 5% - Sensitivity analysis: using best-case or worst-case scenario.	(US$, 1995) Advice + NRT patch $1976/quitter (lifetime) Costs/LYS: Age, men women 35-44, $1902, $3475 45-54, $1822, $3064 55-69, $2456, $3686 (Reference: advice alone)	The nicotine patch is cost-effective and less costly per year of life saved than other widely accepted medical practices.

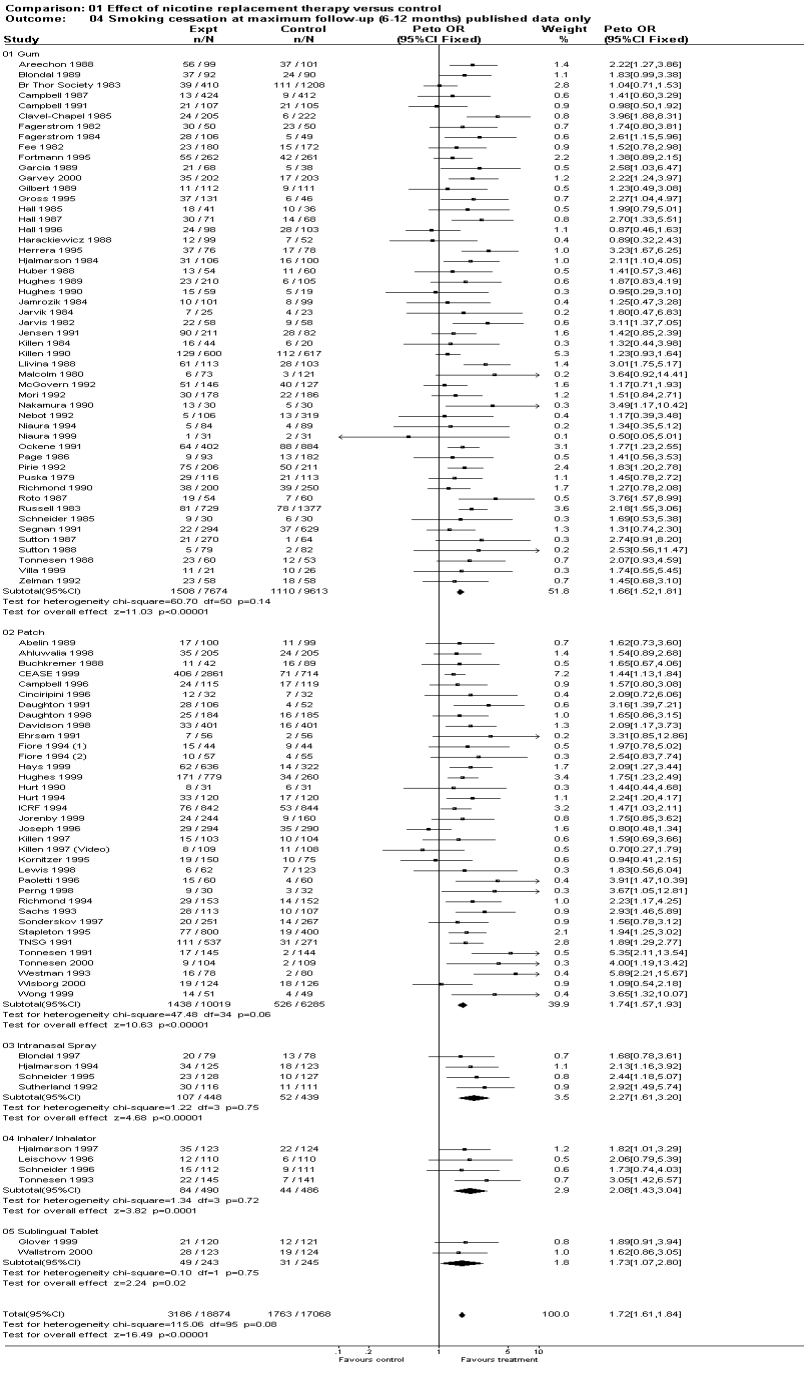
STUDY (YEAR) - COUNTRY - PARTICIPANTS	INTERVENTIONS AND ESTIMATED CESSATION RATES, AND METHODS	METHODS FOR ESTIMATING LYS OR QALYS, AND ADJUSTING FACTOR	CATEGORIES OF COSTS CONSIDERED	- VIEW POINTS - DISCOUNT RATE - DEALING WITH UNCERTAINTY	RESULTS	AUTHORS' CONLUSIONS. COMMENTARY
Buck et al (2000) [192] - Australia - Participants: Smokers among GP patients	- Smokescreen programme (gPs assessed the stage of smoking patients. 26% prepared smokers used NRT gum). Prepared smokers: 21%; Contemplative smokers: 3.25%; Precontemplating smokers: 2% Spontaneous quit rate: 8% (based on control results in trials) (Retrospective data from the programme)	Using no. of quitters as the outcome measure.	Costs of workshop and training, physician time, patient time and travelling, and use of NRT patch.	- Viewpoints: programme organisers, physicians, smokers, or all parties. - Discount rate: not discounted - Sensitivity analysis.	(US$, 1995) Depending on the different perspective: Organisers: $118/quitter Physicians: $279/quitter Smokers: $99/quitter All parties: $496/quitter (Reference: natural practice?)	The Smokescreen programme appears cost-effective when compared to other smoking cessation and health promotion interventions, and illustrates the potential for retrospective cost-effectiveness analysis of interventions. (Table 4 showed a summary of costs/quitter from several studies)
Croghan et al (1997) [193] - US - Participants: 5,544 patients attending Mayo Clinic Nicotine Dependence Centre (NDC) from 04/1988 to 12/1992.	Mayo clinic NDC services: non-physician counselling (60 min), plus possible follow-up session, group therapy, NRT therapy, intensive inpatient treatment etc. - NDC services: 22.2% (6 Mon) Quit rate for those not receiving NDC service: 10.7%, or 7.6%, or 5.5%. Relapse rate: 21.8% after 1 yr, 12.2% after 2 yrs, 1.4% after 3-10 yrs, and 0.0% after 10 yrs. (Following a cohort of patients treated at Mayo Clinic NDC)	Based on data from various sources: published mortality rates for current and former smokers. LYS/quitter: (Discount rate) (3%) 0.80 -1.37; (5%) 0.51 -0.85.	Staff costs; supplies, office and equipment costs; NRT (gum or patch).	- Viewpoint: the payer. - Discount rate: cost: not discounted health benefits: 0%, 3%, 5% - Sensitivity analysis	(US$, 1993) Cost/LYS: (Discount rate) (3%) $2522 - $4303 (5%) $4041 - $6828 (Reference: no NDC services)	Nicotine dependence treatment could be provided in a medical setting in a manner that has practical utility for the patient and the health care provider. The treatment cost of $6828 per net year of life gained is less than many other currently accepted medical interventions. (The cost is not incremental figure, because authors didn't know how much those in the general population who attempt to stop spend on medications or other interventions in producing the 7.6% 1-yr quit rate.)

STUDY (YEAR) **- COUNTRY** **- PARTICIPANTS**	**INTERVENTIONS AND ESTIMATED CESSATION RATES, AND METHODS**	**METHODS FOR ESTIMATING LYS OR QALYS, AND ADJUSTING FACTOR**	**CATEGORIES OF COSTS CONSIDERED**	**- VIEW POINTS** **- DISCOUNT RATE** **- DEALING WITH UNCERTAINTY**	**RESULTS**	**AUTHORS' CONLUSIONS.** **COMMENTARY**
Cummings et al (1989) [194] - US - Participants: A hypothetical group of patients who are smokers and are seen during routine office visits.	- Physician counselling: net 2.7% (95% CI 1.0-4.4%) Relapse rate: 10% (50% for sensitivity analysis) (Meta-analysis of 4 RCTs)	Based on data from Am Cancer Soc 25-state Cancer Prevention Study.	Physician time, patient education material.	- Viewpoint: societal (payers) - Discount rate: cost: not discounted health benefits: 5% (3-7%) - Sensitivity analysis	(US$, 1984) Cost/LYS: men, $705 - $988 women, $1204 - $2058 (Reference: no counselling)	Physician counselling against smoking is at least as cost-effective as several other preventive medical practices and should be a routine part of health care for patients who smoke.
Curry et al (1998) [195] - US - Participants: 90,005 adult enrolees in 7 employers.	Insurance coverage (% for behaviour therapy*NRT): quit * usage rate. - Standard(50-100): 38%*3.5% - Reduced(50-50): 31%*2.4% - Flipped(100-50): 33%*5.3% - Full(100-100): 28%*10.0% (A longitudinal, natural experimental study of insurance coverage and smoking cessation services.)	Quit rate.	Costs to the health plan and users.	- Viewpoints: health plan, or users. -Discount rate: not discounted - No sensitivity analysis	(US$, 1993-4) Average cost per quitter Health plan Total Standard cov: $797, $928 Reduced cov: $801, $1127 Flipped cov: $870, $1036 Full cov: $1171, $1192	Use of smoking cessation services varies according to the extent of coverage, with the highest rates of use among smokers with full coverage. Although the quit rate with full coverage was lower than that with copayment, its effect on the overall prevalence of smoking was greater.
Krumholz et al (1993) [517] - US - Participants: Smoking patients who became clinically stable after acute myocardial infarction.	- Nurse-managed smoking cessation programme after acute MI (initial counselling plus telephone follow-up): 71% - Usual group: 45% Relapse rate: not available but incorporated into the survival curve. (A cohort study)	Modelling of exponential survival curves for smokers and quitters, based on several observational studies. LYS/quitter: 1.7 (0.1-5.0 for sensitivity analysis)	Nurse time, self-help manual and other instructional material.	- Viewpoint: payers - Discount rate: cost: not discounted health benefits: 5%. - Sensitivity analysis	(US$, 1991) Incremental cost/LYS: Baseline, $220 (Reference: usual care)	Over a wide range of estimates of costs and effectiveness, a nurse-managed smoking cessation program after acute myocardial infarction is an extremely cost-effective intervention. (NRT not considered in this programme)

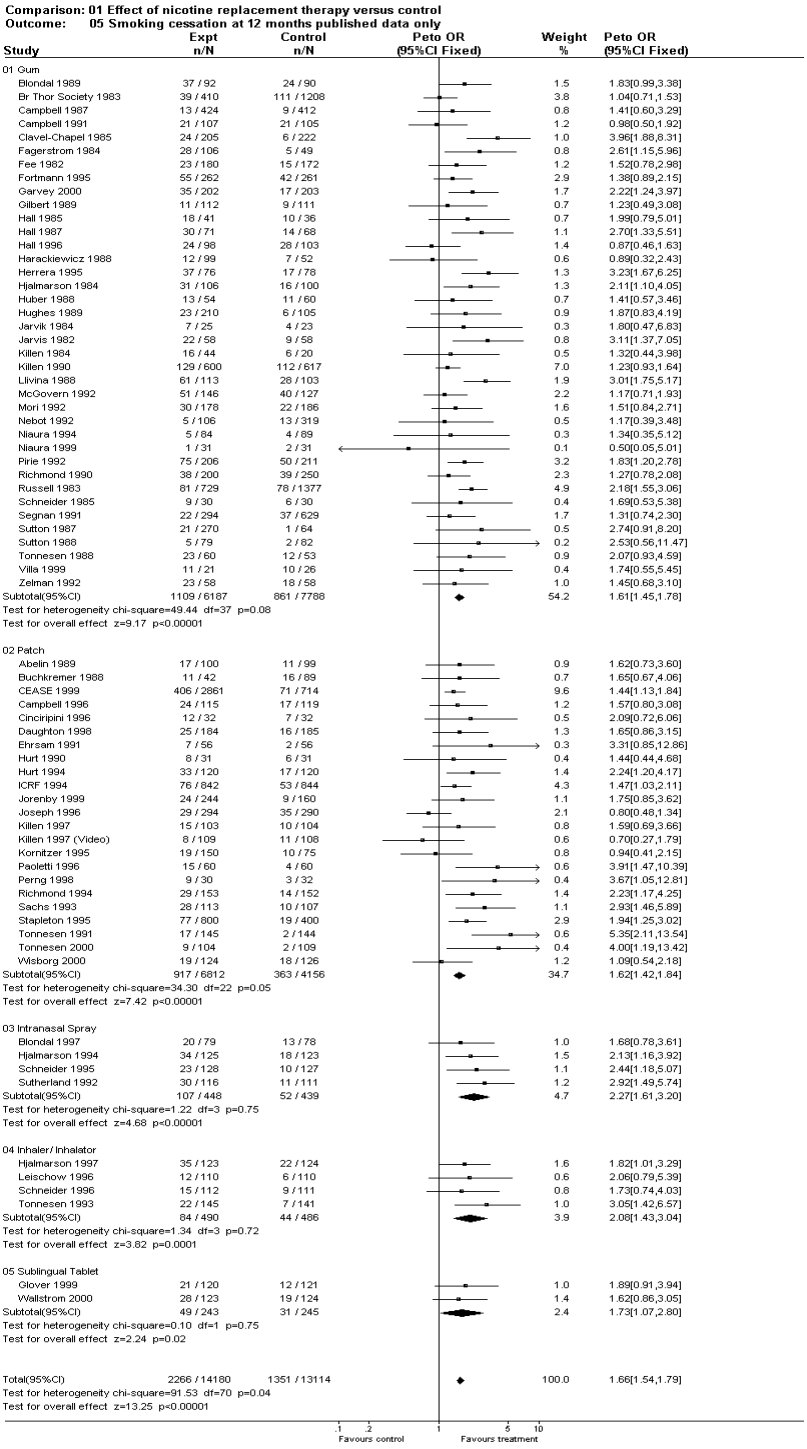
STUDY (YEAR) - COUNTRY - PARTICIPANTS	INTERVENTIONS AND ESTIMATED CESSATION RATES, AND METHODS	METHODS FOR ESTIMATING LYS OR QALYS, AND ADJUSTING FACTOR	CATEGORIES OF COSTS CONSIDERED	- VIEW POINTS - DISCOUNT RATE - DEALING WITH UNCERTAINTY	RESULTS	AUTHORS' CONLUSIONS. COMMENTARY
Nielsen et al (2000) [191] - US - Participants: From a trial by Jorenby et al.	- Placebo 15.6% - Bupropion: 30.3% - NRT: 16.4% - Bupropion + NRT: 35.5% (Data from Jorenby's trial)	Cost-benefit analysis. Benefit (money saved)/quitter: $1654 (0 ~ 1654)	Pharmacological therapy. (Benefits: data based on Mcghan study)	- Viewpoint: Employers - Discount rate: not discounted - Sensitivity analysis.	(US$, 1998) Benefit in the first post-quit yr (the greater the better): - Placebo: $258 - NRT: $26 - Bupropion: $338 - Bupropion + NRT: $178	From an employer's perspective, bupropion is a more cost-beneficial smoking cessation intervention than the nicotine patch, and under most scenarios, bupropion is also more cost-beneficial than placebo.
Halpern et al (2000) [190] - US - Participants: 100,000 health plan members, and 60,000 adult dependants.	No, low, or high level counselling - Bupropion: 13.7%, 15.4%, 23.0% - Bupropion + NRT: 18.9%, 20.6%, 28.2% - NRT patch: 7.7%, 9.4%, 17.0% - No aid: 1.3%, 3.2%, 7.5% Relapse rate: depending on the yr after cessation. (Data from Glaxo Wellcome trials by Hurt et al, and Jorenby et al)	Cost-benefit analysis. Health outcomes estimated based on CDC data about smoking-attributable morbidity and mortality. No. of COPD avoided/quitter: 0.19 No. of deaths postponed/quitter: 0.02	Cost of smoking cessation interventions (based on Cromwell study); short and long term medical expenditure; cost of smoking related diseases; cost of workplace related measures.	- Viewpoint: Insurers, payers and employers. - Discount rate: cost: 3% health outcome: unclear. - Possible to conduct sensitivity analysis.	(US$, 1997) Smoking cessation coverage by managed care organisation: Incremental $1035 ~ $1042/quitter (Reference: without coverage) Benefit-to-cost ratio: 4.1-4.7.	For the managed care scenarios involving coverage of bupropion, for every dollar spent covering smoking cessation, $4.10 to $4.69 in health care cost was saved. For the employer scenarios, for every dollar spent covering smoking cessation, $5.04 to $6.48 was saved. (over a 20-year period).

9.11 FOREST PLOTS OF NRT EFFECTIVENESS DATA

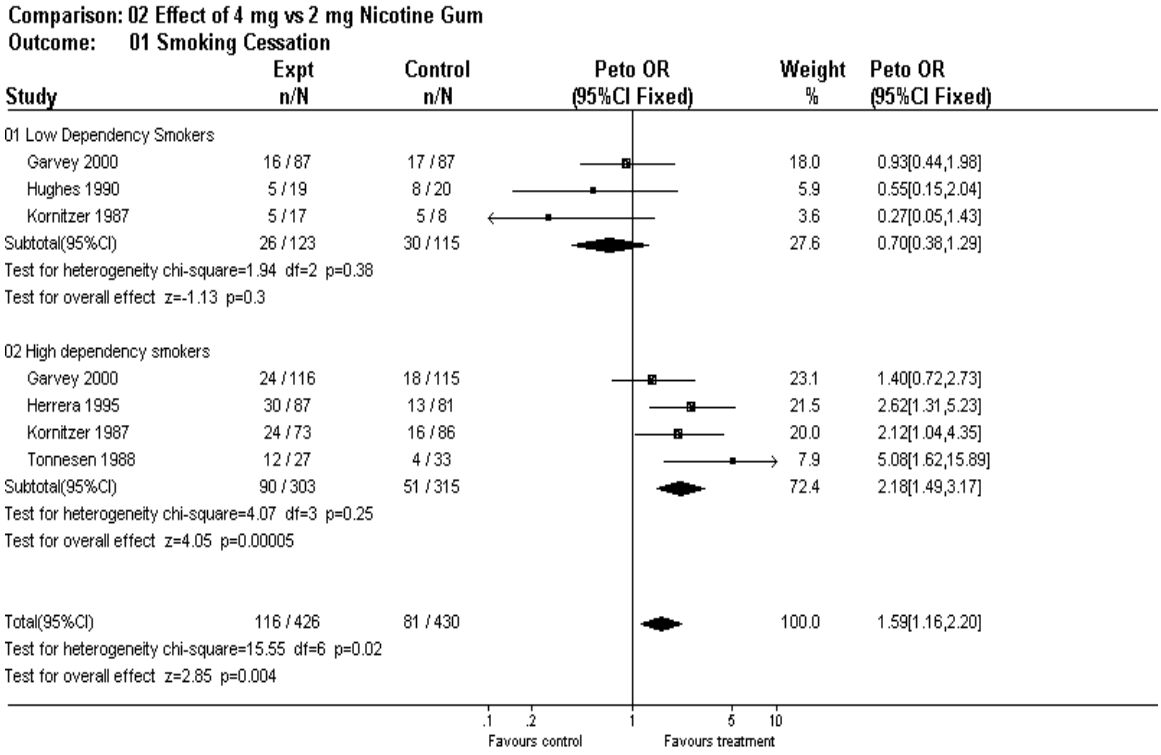
Appendix Figure 1. Abstinence from smoking in smokers followed for at least six months (longest duration of follow-up available): rates and pooled odds ratios (published data only)



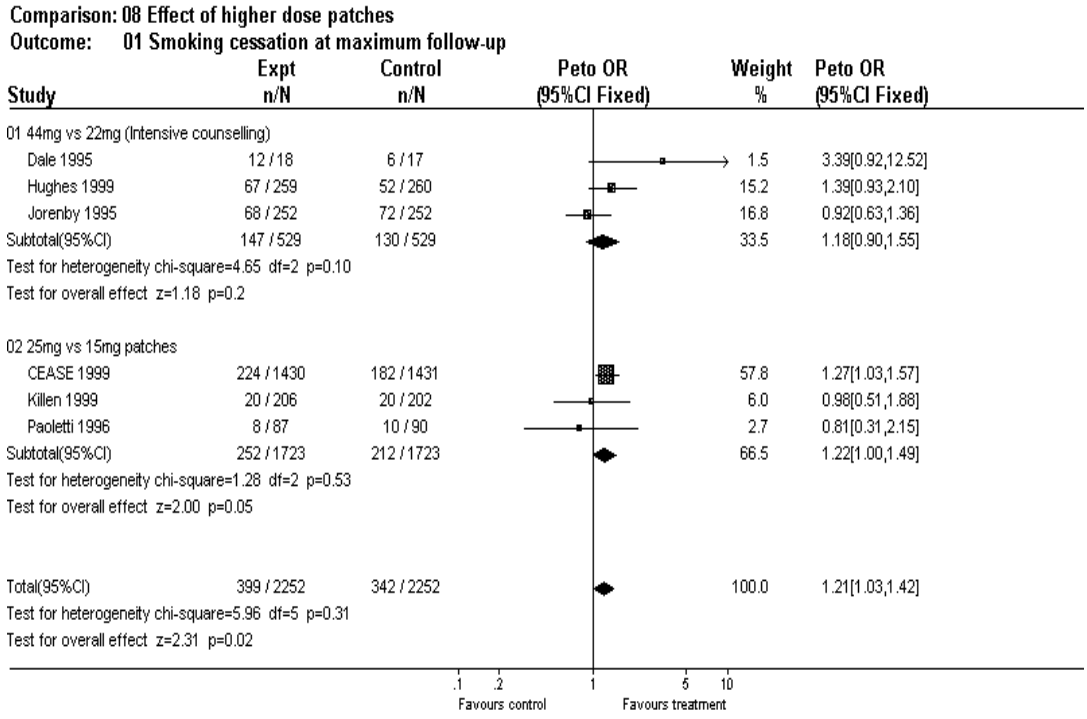
Appendix Figure 2. Abstinence from smoking in smokers followed for at least 12 months: rates and pooled odds ratios (published data only)



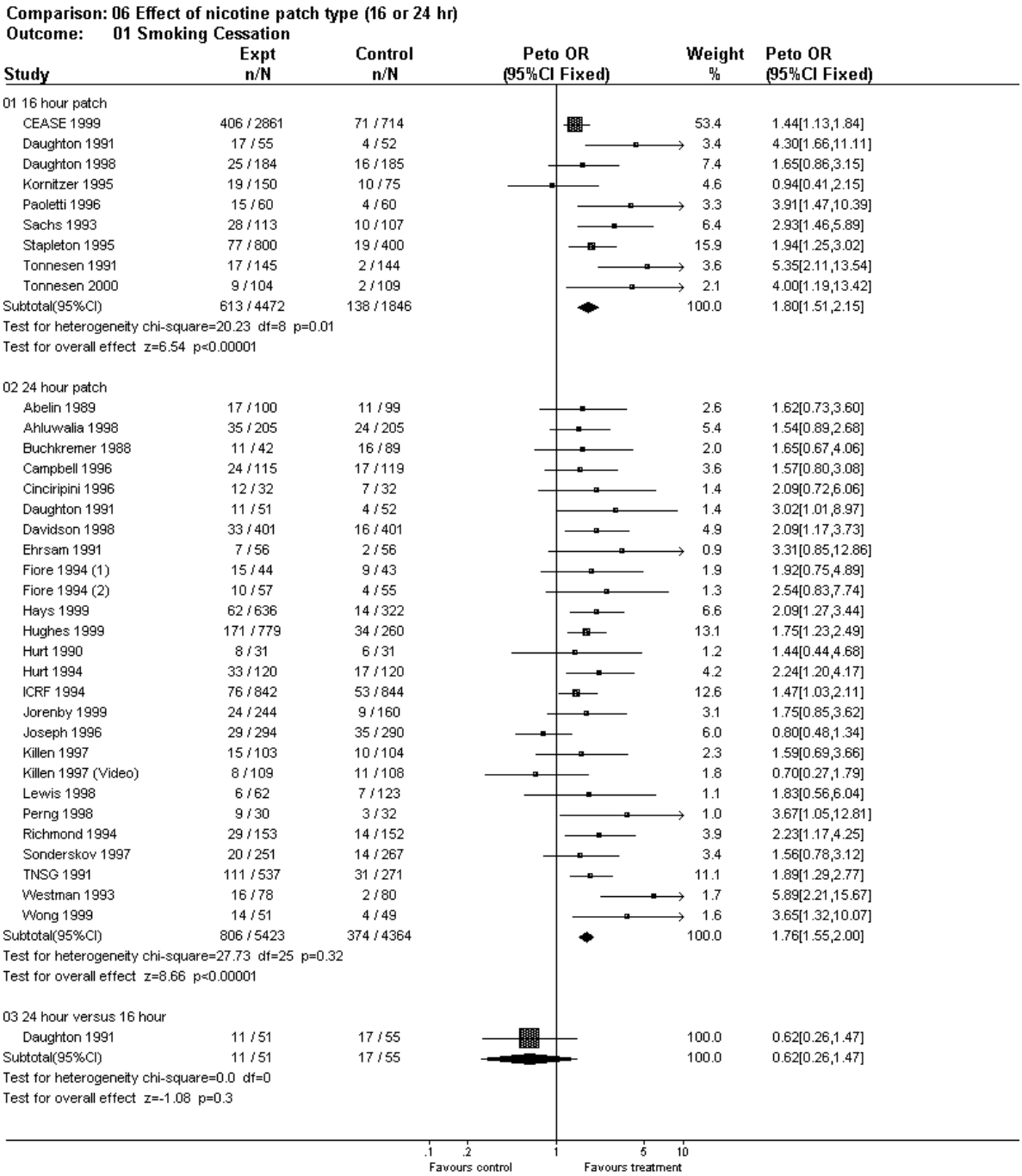
Appendix Figure 3a: Abstinence rates from smoking, high dose versus low dose NRT - rates and pooled ORs (Gum)



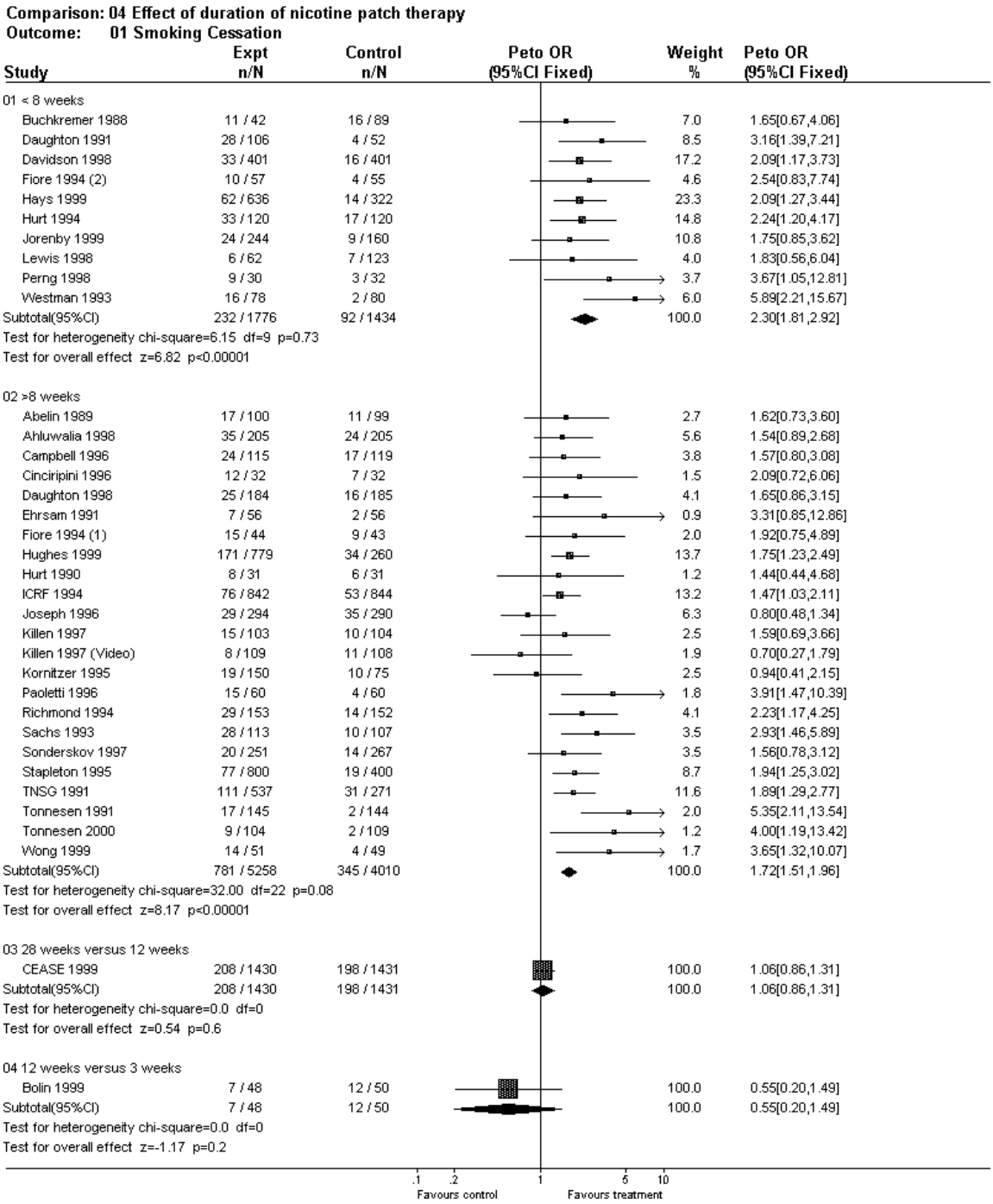
Appendix Figure 3b: Abstinence rates from smoking, high dose versus low dose NRT - rates and pooled ORs (patches)



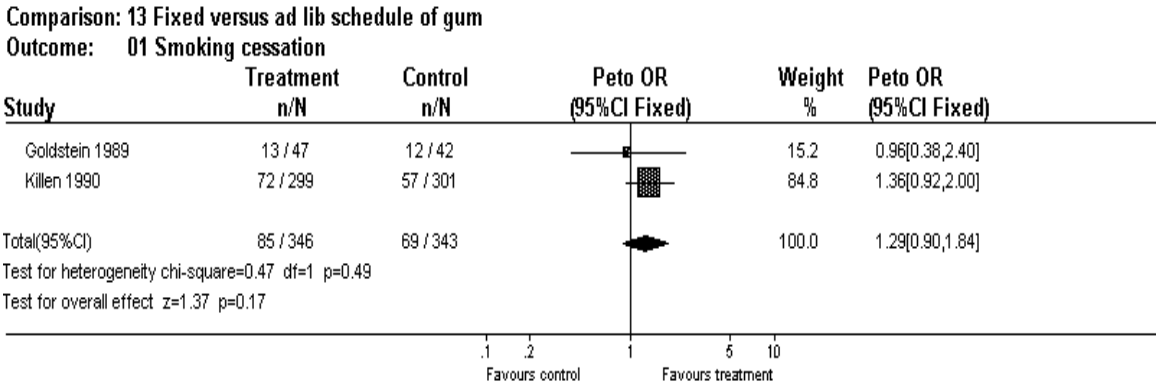
Appendix Figure 4: Abstinence from smoking, effect of patch type (24 or 16 hour)



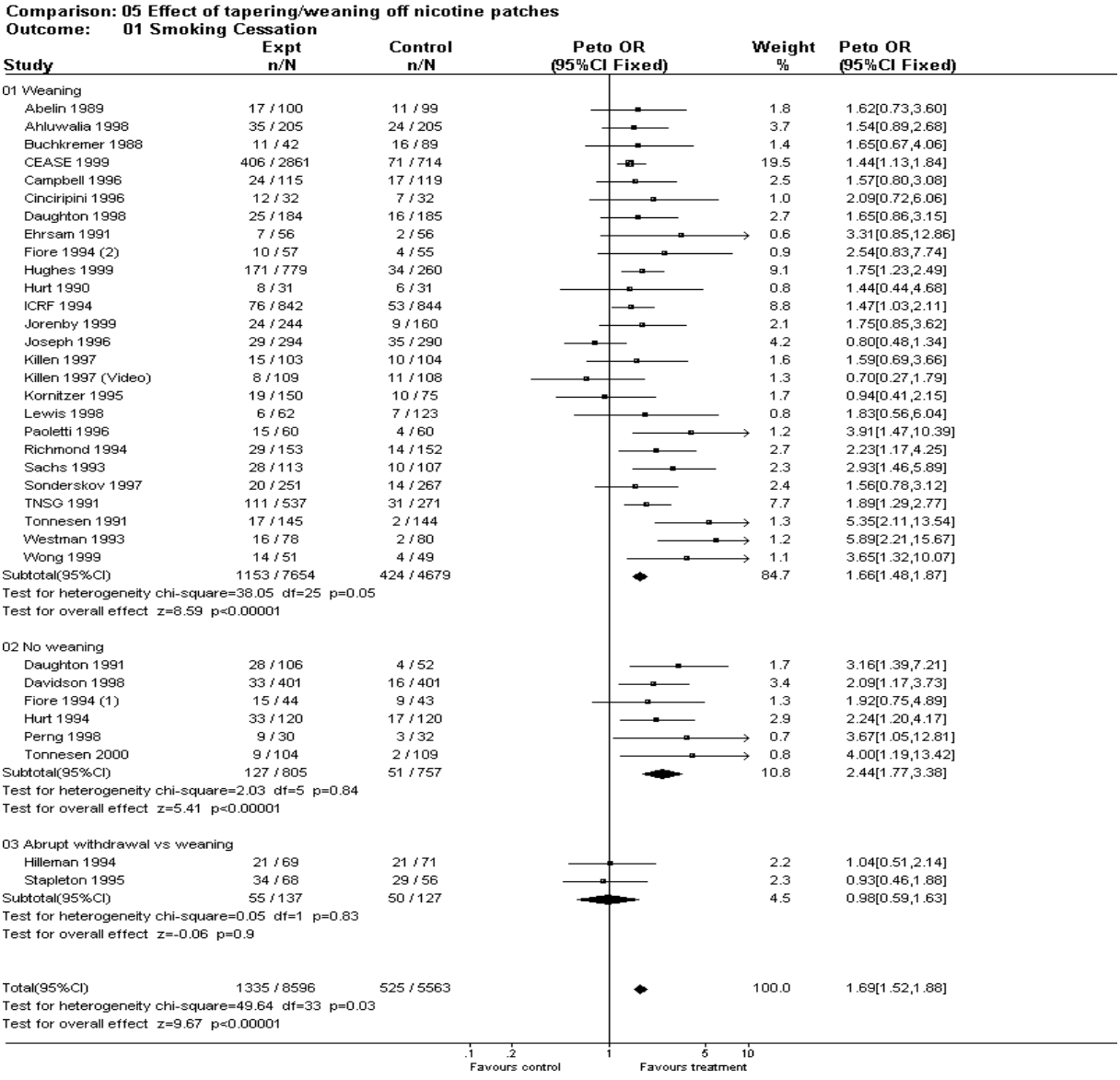
Appendix Figure 5: Abstinence from smoking, effect of duration of NRT therapy



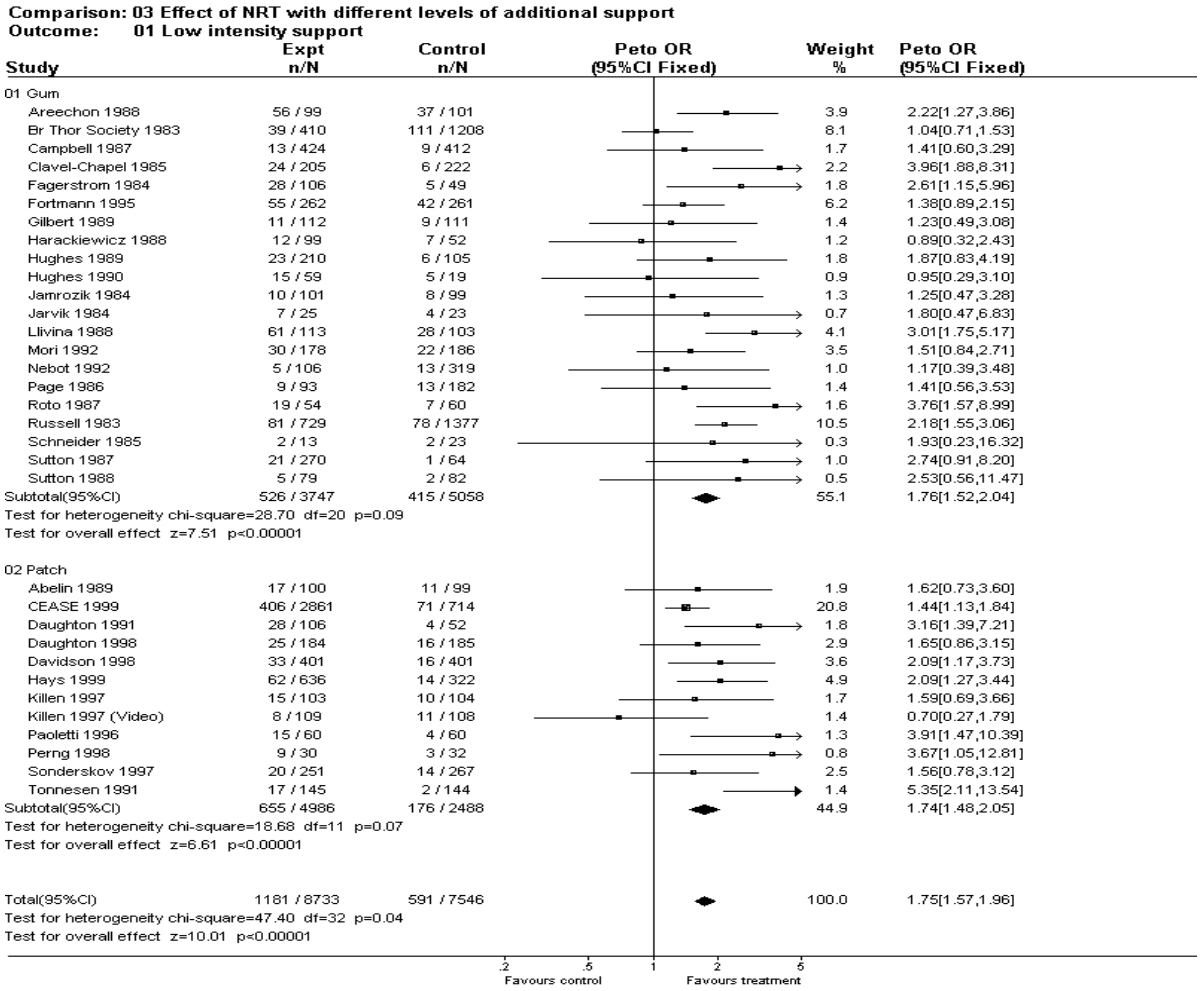
Appendix Figure 6: Abstinence from smoking, fixed regimen vs ad lib use of NRT – rates and pooled ORs



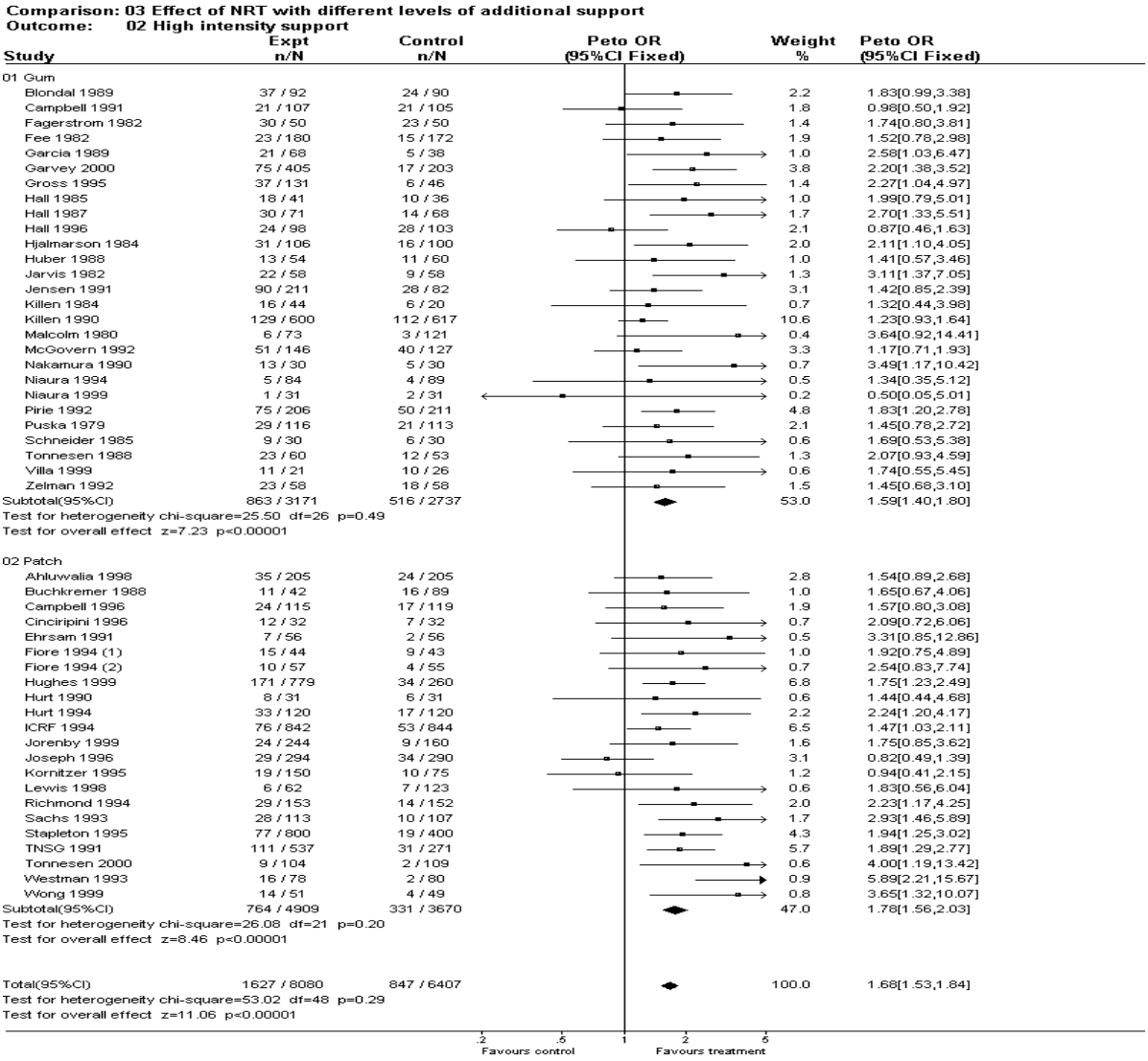
Appendix Figure 7: Abstinence from smoking, abrupt versus gradual withdrawal of NRT – rates and pooled ORs



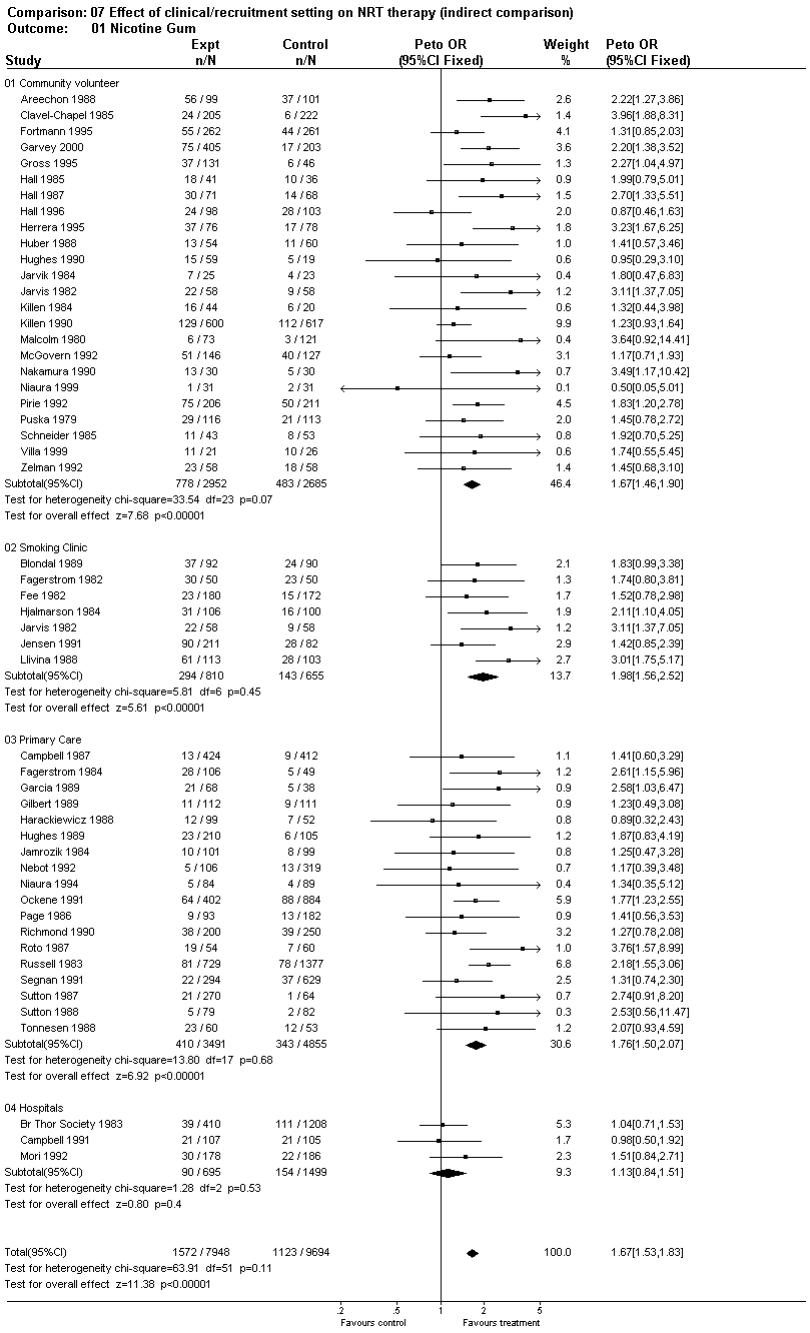
Appendix Figure 8a: Abstinence from smoking, effect of different levels of support – rates and pooled ORs (low intensity)



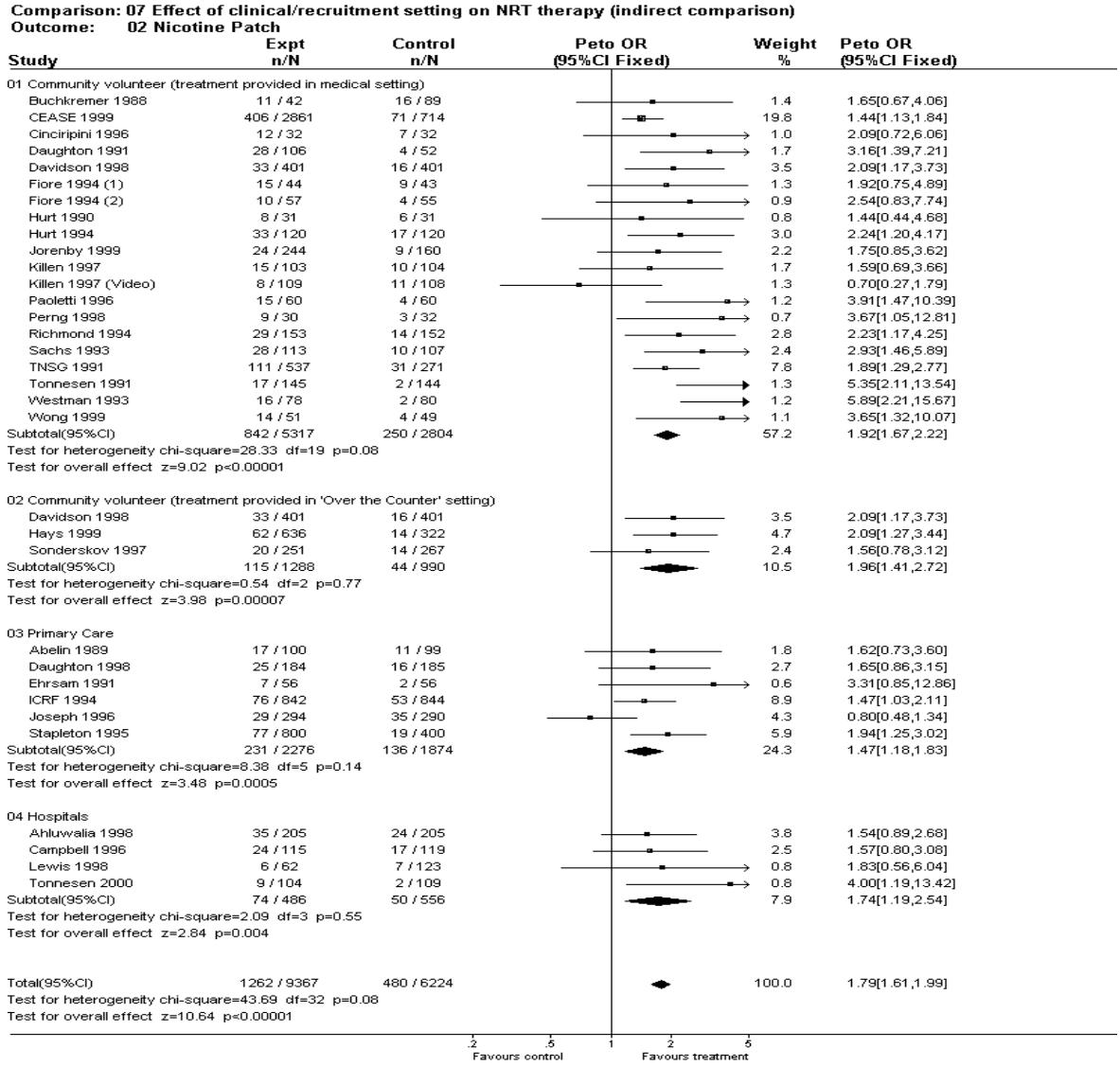
Appendix Figure 8b: Abstinence from smoking, effect of different levels of support – rates and pooled ORs (high intensity)



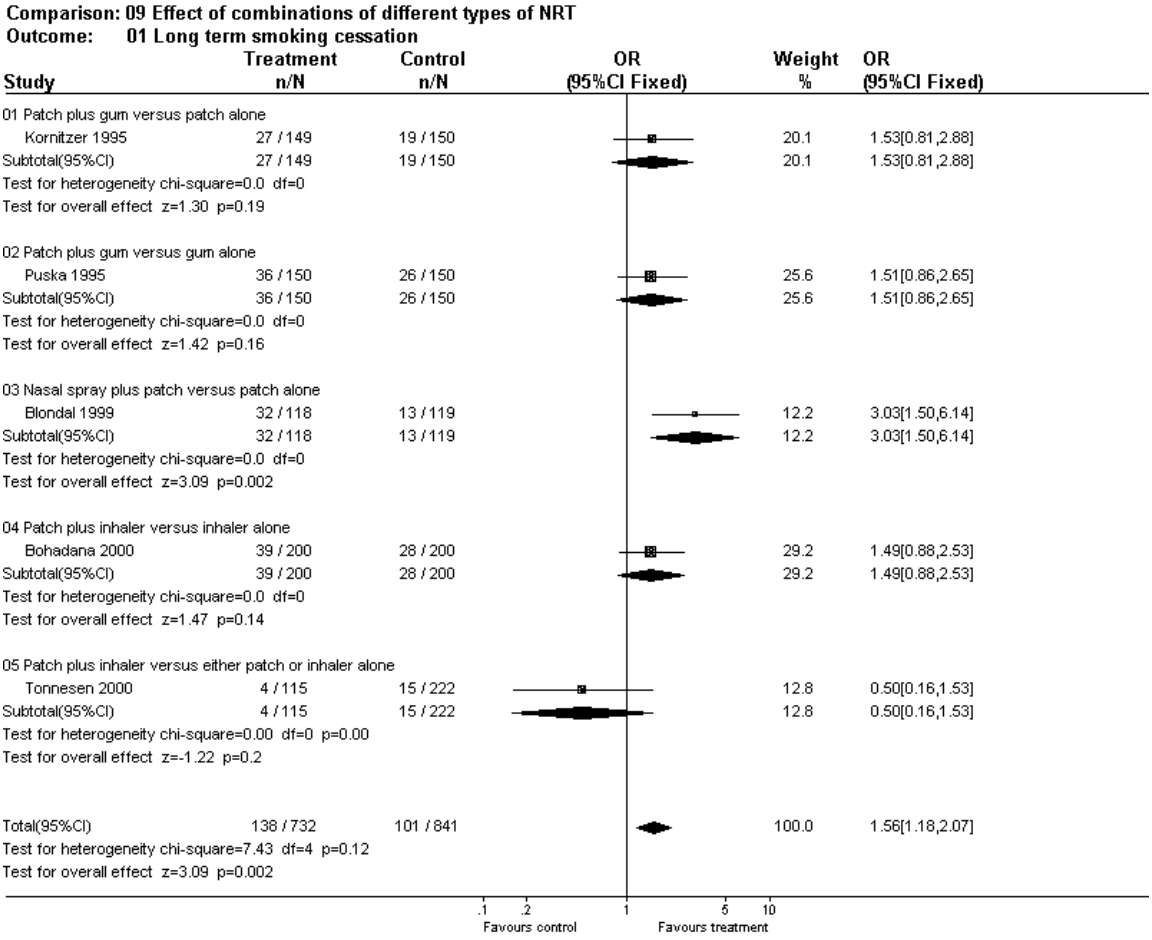
Appendix Figure 9a: Abstinence from smoking, effect of clinical setting – rates and pooled ORs (gum)



Appendix Figure 9b: Abstinence from smoking, effect of clinical setting – rates and pooled ORs (PATCH)



Appendix Figure 10: Abstinence from smoking comparison of various NRT combinations – rates and pooled ORs



9.12 STUDIES INCLUDED IN SYSTEMATIC REVIEWS

9.12.1 Studies included in Cochrane review (NRT for Smoking Cessation [24])

1. Abelin T, Ehrsam R, Buhler Reichert A, Imhof PR, Muller P, Thommen A, et al. Effectiveness of a transdermal nicotine system in smoking cessation studies. *Methods Find Exp Clin Pharmacol* 1989;11:205-14.
2. Abelin T, Buehler A, Muller P, Vesanen K, Imhof PR. Controlled trial of transdermal nicotine patch in tobacco withdrawal. *Lancet* 1989;1:7-10.
3. Abelin T, Ehrsam R, Imhof P, Muller P, Howald H. Clinical experience with a transdermal nicotine system in healthy nicotine-dependent smokers. In: Wilhemsen L, editor. Smoking as a cardiovascular risk factor - new strategies for smoking cessation: Hogrefe & Huber; 1991. pp. 35-46.
4. Ahluwalia JS, McNagny SE, Clark WS. Smoking cessation among inner-city African Americans using the nicotine transdermal patch. *J Gen Intern Med* 1998;13:1-8.
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9.12.2 Studies included in review *A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch* [52]

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