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Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

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.

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

Angioedema Swelling around the eyes, often associated with allergic reactions.

Arthralgia Joint pain.

Case–control study A comparison of exposure to interventions between participants with the outcomes (cases) and those without the outcomes (controls).

Case report A description of a single patient whose case displays interesting features. A case report 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 (e.g. 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 interval Quantifies the uncertainty in measurement. Usually reported as the 95% confidence interval, i.e. the range of values within which one is 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), usual care or nothing.

Cost–benefit 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 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

continued

Glossary *contd*

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 analysis A special form of cost-effectiveness analysis in which utility is measured and the units of effectiveness are quality-adjusted life-years. Utilities can be derived using various methods, including the standard gamble and time trade-off 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 the hands and arms, producing lumps and vesicles or even large blebs full of fluid.

Fagerstrom score Rating of nicotine dependence.

Hazard ratio The hazard (the instantaneous risk of a 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 of related individual studies, to increase statistical power and synthesise the findings of the studies.

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 The odds ratio is similar to relative risk, except that the denominator takes into account the number of individuals within the population 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.

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

Quality of life 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 the individual's physical, mental and social well-being.

continued

Glossary *contd*

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 relative risk greater than one means a person is estimated to be at an increased risk, while a relative risk less than one means a person is apparently at decreased risk. A relative risk of one means there is no apparent effect on risk at all. For example, if the relative risk is four, the result is about four times as likely to happen, and a relative risk of 0.4 means that a result is four times less likely to happen. The relative risk is expressed together with confidence intervals, e.g. relative risk = 3.0 (95% confidence interval, 2.5–3.8). This means that the result is three 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, relative risk = 3.0 (95% confidence interval, 0.5–8.9) means that the result is estimated to be three 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 nine 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.

Stevens–Johnson syndrome A form of erythema multiforme 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 of 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 individual's 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 the health-related qualities of life. Hence, utility has been described as a global measure of health-related quality of life.

Values A measure of the strength of an individual's preference for a given health state or outcome. In contrast to utilities, values reflect preferences without risk (or uncertainty).

List of abbreviations

ACER	average cost-effectiveness ratio*
ANOVA	analysis of variance*
b.d.	twice daily* (*bis die*)
BMI	body mass index*
BTS	Research Committee of the British Thoracic Society*
CI	confidence interval
CNS	central nervous system*
CO	carbon monoxide*
CRD	Centre for Reviews and Dissemination
CSFQ	Changes in Sexual Functioning Questionnaire*
DARE	Database of Abstracts of Reviews of Effectiveness
DBP	diastolic blood pressure*
df	degrees of freedom
DSM-III-R	Diagnostics Statistics Manual, version 3, revised
DSM-IV	Diagnostics Statistics Manual, version 4
ECG	electrocardiogram*
EEG	electroencephalogram*
FBF	forearm blood flow*
FVR	forearm vascular resistance*
HDL	high-density lipoprotein*
HECOS	Health and Economic Consequences of Smoking
ICER	incremental cost-effectiveness ratio
ICRF	Imperial Cancer Research Fund*
IR	immediate release
LDL	low-density lipoprotein*
LOCF	last observation carried forward*
LYS	life-year saved*
MABP	mean arterial blood pressure*
MAOI	monoamine oxidase inhibitor*
MAP	mean arterial pressure*
NA	not applicable*
NRT	nicotine replacement therapy
NS	not significant*
OR	odds ratio
ppm	parts per million
QALY	quality-adjusted life-year
QALYS	quality-adjusted life-year saved*
RCT	randomised controlled trial
RI	resistance index*
RR	relative risk*
SBP	systolic blood pressure*
SD	standard deviation
SE	standard error*
SEM	standard error of the mean*
SPECT	single photon emission computed tomography*
SR	sustained release
t.d.s.	three times daily* (*ter die sumendum*)
TNSG	Transdermal Nicotine Study Group*
TPRI	total peripheral resistance index*

* Used only in tables

Executive summary

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. Nicotine replacement therapy (NRT) and bupropion sustained-release formulation (SR) (Zyban®) are two pharmacological agents available to aid smokers in their attempts to achieve smoking cessation.

Objectives

The aim of this review was to assess the clinical effectiveness, cost-effectiveness and adverse effects of bupropion SR and NRT for smoking cessation. The effects of therapy in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit were not assessed.

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 and exclusion criteria

Two reviewers independently screened all titles and abstracts for relevance and made final decisions regarding the inclusion and exclusion criteria of studies based on full paper copies of manuscripts. Studies were assessed according to predefined 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 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-RCTs, case-controlled studies, uncontrolled studies and surveillance studies, the primary objective of which was the investigation of the adverse effects, tolerability or safety of bupropion SR or bupropion 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 predefined 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. Subgroup and sensitivity analyses are reported where data are available. For the assessment of adverse events and safety the summary was mainly a narrative one. In 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 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 investigating the use of NRT gum and NRT patches. Despite this, there are no data to indicate that other forms of NRT are less efficacious. There are no data to indicate subgroup differences in the response to NRT.

There is clear evidence that bupropion SR is more effective than placebo. There is evidence from single subgroup populations that bupropion SR is as effective in smokers with chronic obstructive pulmonary disease, 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 relates to 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) reported in this review are newly identified. The adverse events resulting in withdrawal from treatment with bupropion SR are the same as those for the IR formulation (skin disorders (mainly rash), insomnia, tremor, headache, dry mouth, 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 and duration of treatment, and differences in response between depressed and non-depressed patients. Significantly, the side-effect profile of bupropion SR does appear to be better than that of the IR formulation.

This review identified seizure as the most significant and important potential adverse effect of bupropion SR, as had already been recognised. 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 the 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 £1000) 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:

- advice or counselling only (including general practitioner advice and more intensive counselling by other health professionals)
- advice plus NRT
- advice plus bupropion SR
- advice plus NRT and bupropion SR.

The results of this decision analysis modelling are broadly similar to those found in 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-year saved is about £1000–2400 for NRT, £640–1500 for bupropion SR and £900–2000 for NRT plus bupropion SR.

The estimated cost of the smoking-cessation programme to the NHS in England and Wales would be about £67 to 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 £500–1500).

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 available data on the relative efficacy of bupropion SR and because the cost of adverse effects of bupropion SR were not considered 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 motivational support is probably involved.
- 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 the methods used or the assumptions involved, the results of existing economic evaluations and the model developed in this review consistently suggest that smoking-cessation interventions, including the use of NRT and/or bupropion SR, are relatively cost-effective in terms of the cost per life-year saved. The worst-case scenarios still provide estimates of cost-effectiveness better than many other medical interventions.

Recommendations for research

Studies that compare the effectiveness of NRT with that of bupropion SR are needed. Ideally, these studies should include a high level of motivational support.

To increase the effectiveness of all smoking cessation agents the questions to be asked include:

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

Chapter 1

Aim of the review

The aim of this review was to address the clinical effectiveness, cost-effectiveness and adverse effects of bupropion sustained-release formulation (SR) and nicotine replacement therapy (NRT) for smoking cessation. It did not address the effects of these interventions in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit.

Chapter 2
Background

The underlying health problem

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 UK, with more than 120,000 deaths of people aged over 35 years attributable to smoking. Furthermore, exposure to second-hand smoke by non-smokers 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 fetal death.[1] Furthermore, women who smoke during pregnancy place the fetus 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 17,000 children under the age of 5 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, intermittent claudication and chronic obstructive pulmonary disease.[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 do 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*-nitrosamine, 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 1970s and 1980s has levelled out since the 1990s. 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 among men and women fell by 1% and 2%, respectively.[5] Figures from 1998 also suggest that smoking is most prevalent among those aged 20–24 years (42% for men, 39% for women) and lowest among men and women aged 60 years and over (16% for both men and women).[5]

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 1 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 years 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 20–90%.[7] The risk of developing oral cancer is cut in half after only 3–5 years, and after 10 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. Thus the benefits of stopping smoking are great.

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 had successfully abstained from smoking for a period of 1 month or more and only 2.5% of all smokers achieved permanent abstinence each year.

Smokers develop tolerance to some of the behavioural and sympathomimetic effects of nicotine over time, a process called neuro-adaptation. 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 2–4 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.

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 complicate matters further, the adverse events associated with any smoking-cessation intervention have to be differentiated from the unpleasant effects of stopping smoking (i.e. withdrawal symptoms). The question of whether the adverse effects of NRT and bupropion SR are a significant deterrent to their use in smoking cessation, particularly in otherwise healthy people, is addressed in this review.

Current service provision

NRT

The following NRTs are available in the UK.[10]

- Nicotine transdermal patches:
  - 5 mg, 10 mg, 15 mg (Nicorette®, Pharmacia)
  - 0.7 mg/cm^2 (10 cm^2, 20 cm^2, 30 cm^2) (Nicotinell®, Novartis Consumer)
  - 7 mg, 14 mg, 21 mg (NiQuitin CQ®, SmithKline Beecham*).
- Nicotine chewing gum:
  - 2 mg, 4 mg (Nicorette, Pharmacia; Nicotinell, Novartis Consumer).
- Nicotine 2 mg sublingual tablet (Nicorette, Microtab Pharmacia).
- Nicotine 1 mg lozenge (Nicotinell, Novartis Consumer Health).
- Nicotine 2 mg and 4 mg lozenge (NiQuitin, SmithKline Beecham).
- Nicotine 10 mg inhalation cartridge plus mouthpiece (Nicorette, Inhalator Pharmacia).
- 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 NHS.[10]

Bupropion SR

In June 2000 the Medicines Control Agency granted a licence for bupropion hydrochloride SR (Zyban®, Glaxo Wellcome*) as a prescription-only drug to be used for smoking cessation (with motivational support) in the UK.[11] In the USA this drug is also indicated as an antidepressant and licensed as Wellbutrin®.

Description of the intervention

NRI

NRT 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

* During the time that this review was being conducted, Glaxo Wellcome and SmithKline Beecham merged to form GlaxoSmithKline.

of cigarettes smoked per day), which should be used for 3 to 4, 6 or 8 weeks (according to preparation). All preparations recommend a gradual reduction in the strength of patch used before completing the course in approximately 3 months (10–13 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/day. Lozenge use should be withdrawn gradually after 3 months and the maximum period of treatment should be 6 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 3 months followed by a gradual withdrawal, giving an overall therapy period of 6 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 8 weeks, followed by a reduction by half over the next 2 weeks and reducing to zero over the 2 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 8 weeks and then be reduced gradually to zero over the next 4 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 myocardial infarction, 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 period after myocardial infarction and 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]

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, 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; corticotrophin; and lobeline.[15,16]

According to the 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 3 days increasing to two tablets daily, allowing a minimum of 8 hours between doses, has been changed to one tablet (150 mg) for 6 days before commencing the higher dose. Treatment with bupropion SR should start while the patient is still smoking since it takes approximately 7 days of treatment before bupropion blood levels achieve steady state.[17] Patients

should set a target to stop smoking 7–14 days after initiating treatment and should continue taking bupropion SR for 7–9 weeks.[10]

Bupropion SR is contraindicated 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 central nervous system tumour; abrupt withdrawal from alcohol or benzodiazepines; severe hepatic cirrhosis; treatment with monoamine oxidase inhibitors; and a history of bipolar disorder.[18]

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/day 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.[18]

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 gastrointestinal 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 pruritus, urticaria, angioedema, and dyspnoea have been reported, and there have been rare reports of erythema multiforme, Stevens–Johnson syndrome and anaphylactic shock. Symptoms resembling serum sickness have also been reported.[18]

Chapter 3
Methods

This 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 profile of adverse events of bupropion SR and NRT. In addition to RCTs, the types of studies considered for inclusion were non-RCTs, 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.

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 clinical effectiveness, cost-effectiveness and safety of bupropion SR (Zyban) and 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 1.

The search strategies were devised by the Information Service Team at the NHS Centre for Reviews and Dissemination (CRD), 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 focused on identifying all relevant **systematic reviews** in the area.

A search strategy was then devised to identify any newly published **RCTs** 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 2000 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:

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

Full details of all databases searched and search strategies used are provided in appendix 1. Information on the database hosts and date ranges searched for each database is also included.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts for relevance. Full paper manuscripts of any titles or abstracts that were of potential relevance were obtained, and the relevance of each article assessed according to predefined criteria. Systematic reviews and other studies, which did not fulfil all the criteria, were excluded and their bibliographic details listed, with the reason for exclusion (see appendix 2). 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.

Interventions

Clinical effectiveness and cost-effectiveness studies

Studies of bupropion (150 mg/day or 300 mg/day) immediate-release (IR) and 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.

The types of NRT used in the studies were:

- 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 acupuncture.

Adverse-effects studies

As clinical experience with bupropion SR as an aid to smoking cessation is limited, studies involving 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.

Participants

Clinical effectiveness and cost-effectiveness studies

Participants were smokers of any age or gender. Where possible and appropriate, subgroups were identified.

Adverse-effects studies

For adverse effects of bupropion SR, data related to any participants taking bupropion (IR or SR) for any indication were 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 were 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.

Study design

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 were 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)[19] (see appendix 4) were considered further for inclusion in the review. As stated below, only systematic reviews that included only studies with a minimum of 6 months follow-up or newly identified RCTs that met this criterion were included in the review.

Economic evaluations

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

Adverse-effects studies

For the evaluation of adverse events a broader range of studies, in addition to systematic reviews, was considered. These included non-RCTs, 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 the primary objective of which 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.

Outcome measures

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 were examined separately. Greater emphasis was placed on data derived from longer follow-up periods. Where possible, continued abstinence rather than point prevalence was 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.

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 (QALY) saved compared with no or alternative interventions. Studies reporting the cost–benefit of interventions for smoking cessation were also included.

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

Adverse-effects studies

The incidence and severity of all adverse events were reviewed.

Data extraction strategy

All relevant data, including study details, study quality, details of participants, interventions and results, were extracted by one reviewer into an Access database, and independently checked for accuracy by a second reviewer (example extraction sheets shown in appendix 3). 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 given in appendix 3.

Quality assessment strategy

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

The quality of systematic reviews of effectiveness and/or side-effects have been assessed using criteria developed for DARE (see appendix 4).[19]

The quality of RCTs was assessed using criteria based on CRD Report No. 4 (see appendix 4).[20] 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 4).[21] 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, e.g. 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 course of this review, the quality assessment using the cohort study checklist

is still appropriate. This information is presented in this report in table form and summarised within the text.

The protocol stated that criteria based on the Drummond checklist would be used to assess the quality of economic evaluations (see appendix 4).[22] However, this was not done, due to the limited utility and time constraints. In this review, the economic evaluation of NRT and bupropion SR for smoking cessation was focused on the development of a decision analysis model.

Methods of analysis and synthesis

Clinical effectiveness studies

Details of the extracted data and the 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 were conducted to assess differences in effectiveness between different participant groups.

Economic evaluations

Included studies of the economic evaluation of bupropion SR and/or NRT are grouped according to type of evaluation (cost-effectiveness, cost–utility, cost–benefit), type of outcomes, type of comparators and country of origin. Economic evaluation studies conducted in the UK with an NHS perspective are particularly emphasised.

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

Two commonly used approaches for estimating the life-years saved from the number of quitters are:

- the use of an established computer model PREVENT
- a comparison of mortality between smokers and ex-smokers or non-smokers based on data from health surveys.

These approaches were assessed based on the existing literature, and their outcomes are compared in the review.

Costs of smoking-cessation interventions may include costs to providers of smoking-cessation interventions, and 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 NHS. 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 healthcare for smokers who stop smoking. It is relatively straightforward to measure the direct costs of a programme, but it is very complicated to measure its impact on long-term healthcare spending.[23] In this review the research into the impact of smoking-cessation interventions on healthcare spending, each linked to outcomes (QALYs and quitters), has been summarised, but the modelling was focused on the short-term direct costs of a 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 the usage of bupropion SR, NRTs and other smoking-cessation interventions needs to be estimated. For example, the model proposed by Parrott and co-workers[23] 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.[23] In another model, the Health and Economic Consequences of Smoking (HECOS) model, the default proportion of usage of different interventions for smoking cessation in the UK is 25% for pharmacological therapy, 10% for general practitioner (GP) advice, 2% for group sessions and 63% for willpower (no intervention).[24] The estimates and assumptions in the literature about the proportions of smokers who attempt to quit and usage of different interventions were 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 (i.e. costs at 6% per annum, long-term health benefits at 1.5% per annum). Sensitivity analyses

were conducted to explore the impact of uncertainty in estimating incremental cost and effectiveness, and the choice of different rates of discounting.

Adverse-effects studies

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

Chapter 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 2, together with the reason for their exclusion. In addition, three company submissions were received. A total of 17 references relevant to the economic evaluation of bupropion SR and NRT in smoking cessation were identified from the literature searches and assessed.

Clinical effectiveness

NRT

Two systematic reviews,[25,26] five newly identified published RCTs[27–31] and two unpublished RCTs (commercial in confidence data)[32,33] met the criteria for inclusion in the review.

Systematic reviews

Description of systematic reviews

Of the two systematic reviews, one[26] was conducted by the Cochrane Tobacco Addiction Review group, and the other[25] is a US Public Health Service report. The US report includes only articles published in peer-reviewed journals between 1 January 1975 and 1 January 1999 and, therefore, is less comprehensive and less up to date than the Cochrane Review. Therefore, only the NRT data from the Cochrane Review were used in this report.[26]

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 6 months, were included in the Cochrane Review.[26] In each study the strictest available definition of abstinence was used and, wherever possible, the 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 was not an objective of the present review and, therefore, these data are not discussed further.

One-hundred and eight RCTs and quasi-RCTs were included in the Cochrane Review (for most of the references, see appendix 12). 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 the day of the week or of 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 were 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).[26]

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 settings. Five were in workplace settings, two in a university clinic and one in a Veteran's Affairs Medical Centre. Eight studies were undertaken 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 8 (*Table 68*). The Cochrane Review was a good-quality systematic review.[26] 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, which 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. Appropriate meta-analyses with tests for heterogeneity were performed and the results are presented in full.

Newly identified RCTs

Description of newly identified RCTs

Five newly identified published RCTs of NRT were included.[27–31] One was a study of NRT patches in pregnant women,[31] one was a comparison of NRT patch plus telephone support with NRT patch alone[30] and the other three were comparisons of NRT with another active treatment. (It should be noted that one of these three studies[29] was included in the Cochrane Review,[26] but only as a comparison with placebo, and not as a comparison with an active intervention included here.) In addition, two unpublished studies were identified.[32,33] One was a placebo-controlled comparison of 2 mg and 4 mg dose NRT lozenges and one was a comparison of NRT gum (4 mg) with bupropion SR. Limited details of these unpublished studies are presented in appendix 5 (*Table 28*). 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 8 (*Table 62*). None of the five published trials fully reported the randomisation procedure. Three of the trials were reported to be double-blind,[28,29,31] but one study was not blinded between the two treatments of interest (NRT and naltrexone).[29] The other two studies were unblinded.[27,30] Concealment of allocation was judged to be adequate in two trials[29,31] and unclear in two.[28,30] Only one study reported using a power calculation *a priori* for sample size.[28] 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.[27] One trial provided weekly or biweekly 15–20 minute counselling sessions for both study groups throughout the treatment period,[29] one study[31] included four clinic visits or telephone calls, and one study[30] included telephone support in one treatment arm only. All the studies reported the statistical methods used, but only one reported the degree of variability around the point estimates.[28] All studies undertook intention-to-treat analyses, although in one study withdrawals were not clearly reported.[27] 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.[31] The definition of abstinence varied. Two studies relied on self-reports and measured carbon monoxide levels.[28,30] One trial used daily diary records, with confirmation with carbon monoxide measurements at every assessment (carbon monoxide level no more than 8 ppm).[29] Another trial used carbon monoxide levels less than 4 ppm to determine abstinence.[25] The study in pregnant women[29] used self-report and saliva cotinine levels.

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

All the results presented in this section were derived from systematic reviews that 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 11. These are derived from the Cochrane Review.[26] The two newly identified unpublished RCTs[32,33] that could have updated this review are unpublished and therefore were not included.

If the results are pooled using a random effects model the odds ratio (OR) for any NRT is 1.77 (95% confidence interval (CI), 1.63 to 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 to 1.86) or, using a random effects model, OR = 1.79 (95% CI, 1.65 to 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 11.

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

If the unpublished study is included, the result for any NRT is Peto OR = 1.69 (95% CI, 1.57 to 1.82) or, using a random effects model, OR = 1.74 (95% CI, 1.58 to 1.91).

TABLE 1 *Abstinence from smoking in smokers followed for at least 6 months (longest duration of follow-up available): rates and pooled ORs (published data only)*

Type of NRT	Abstinence rate		Peto OR (95% CI)	*p* value for comparison	No. of studies in meta-analysis	χ^2 test for heterogeneity (df; *p*)
	On treatment	On placebo or no treatment				
Gum	1,508/7,674	1,110/9,613	1.66 (1.52 to 1.810)	< 0.00001	51	60.70 (50; 0.14)
Patch	1,438/10,019	526/6,285	1.74 (1.57 to 1.93)	< 0.00001	35	47.48 (34; 0.06)
Inhaler	84/490	44/486	2.08 (1.43 to 3.04)	0.0001	4	1.34 (3; 0.72)
Nasal spray	107/448	52/439	2.27 (1.61 to 3.20)	< 0.00001	4	1.22 (3; 0.75)
Sublingual tablet/ lozenge	49/243	31/245	1.73 (1.07 to 2.80)	0.02	2	0.10 (1; 0.75)
Any	3,166/18,874	1,763/17,068	1.72 (1.61 to 1.84)	< 0.00001	96	115.06 (95; 0.08)

df, degrees of freedom

TABLE 2 *Abstinence from smoking in smokers followed for at least 12 months: rates and pooled ORs (published data only)*

Type of NRT	Abstinence rate		Peto OR (95% CI)	*p* value for comparison	No. of studies in meta-analysis	χ^2 test for heterogeneity (df; *p*)
	On treatment	On placebo or no treatment				
Gum	1,109/6,187	861/7,788	1.61 (1.45 to 1.78)	< 0.00001	38	49.44 (37; 0.08)
Patch	917/6,812	363/4,156	1.62 (1.42 to 1.84)	< 0.00001	23	34.30 (22; 0.05)
Inhaler	84/490	44/486	2.08 (1.43 to 3.04)	0.0001	4	1.34 (3; 0.72)
Nasal spray	107/448	52/439	2.27 (1.61 to 3.20)	< 0.00001	4	1.22 (3; 0.75)
Sublingual tablet/ lozenge	49/243	31/245	1.73 (1.07 to 2.80)	0.02	2	0.10 (1; 0.75)
Any	2,266/14,181	1351/13,114	1.66 (1.54 to 1.79)	< 0.00001	71	91.53 (70; 0.04)

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 heterogeneous 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 subgroups:

- smokers with lung disease
- smokers with cardiovascular disease
- smokers with pulmonary or vascular disease
- smokers with smoking-related diseases (not specified)
- pregnant women smokers.

These data are presented graphically in appendix 11.

Two studies of **smokers with lung disease** were included in the analysis.[35,36] For details of these studies the reader is referred to the Cochrane Review.[26] 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 to 9.15; $p = 0.002$). These data are presented graphically in appendix 11.

There was only one study that included only **smokers with cardiovascular disease** in the analysis.[37] For details of this study the reader is referred to the Cochrane Review.[26] 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 to 1.34; $p = 0.4$).

There was only one study that included only **smokers with pulmonary or vascular disease** (mixed population) included in the analysis.[38] For details of this study the reader is referred to the Cochrane Review.[26] 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 to 1.53; $p = 0.08$).

Two studies of **smokers with smoking-related diseases (not specified)** were included in the analysis.[39,40] For details of these studies the reader is referred to the Cochrane Review.[26] 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 to 1.94; $p = 0.3$).

One study investigated the effectiveness of NRT versus placebo in **pregnant women smokers**.[31] Details of this study are given in appendix 5 (*Table 28*). At the fourth prenatal visit (scheduled for 4 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 the 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 to 2.18).

Other comparisons

Other comparisons were made within the Cochrane Review.[26] These are summarised below and presented graphically in appendix 11. A comparison of 4 mg versus 2 mg gum in high dependency smokers (i.e. smokers highly dependent on nicotine, usually having a Fagerstrom score of 7 or more) included four trials, giving an OR of 2.18 (95% CI, 1.49 to 3.17; $p = 0.00005$; test for heterogeneity, $\chi^2 = 4.07$, 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 to 1.55; $p = 0.2$; test for heterogeneity, $\chi^2 = 4.65$, 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 to 1.49; $p = 0.05$; test for heterogeneity, $\chi^2 = 1.28$, df = 2, $p = 0.53$). The results were dominated by the inclusion of one large trial.

The Cochrane Review[26] 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 to 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 to 2.15; $p < 0.00001$; test for heterogeneity, $\chi^2 = 20.23$, 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 to 2.00; $p < 0.00001$; test for heterogeneity $\chi^2 = 27.73$, df = 25, $p = 0.32$).

The effect of duration of NRT has only been compared directly in two RCTs. One study compared 28 weeks of therapy with 12 weeks (OR = 1.06; 95% CI, 0.86 to 1.31; $p = 0.6$) and the other compared 12 weeks of therapy with 3 weeks (OR = 0.51; 95% CI, 0.20 to 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 to 2.92; $p < 0.00001$; test for heterogeneity, $\chi^2 = 6.15$, df = 9, $p = 0.73$). Pooled data from 23 studies with longer than 8 weeks of therapy gave an OR of 1.72 (95% CI, 1.51 to 1.96; $p < 0.00001$; test for heterogeneity, $\chi^2 = 32.00$, 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 to 1.84; $p = 0.17$; test for heterogeneity, $\chi^2 = 0.47$, 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 to 1.63; $p = 0.9$; test for heterogeneity, $\chi^2 = 0.05$, 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.[26] Low-intensity support was defined as part of the provision of routine care in the Cochrane Review.[26] High-intensity support was defined as any support that involved at least 30 minutes 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 to 1.96; $p < 0.00001$; test for heterogeneity, $\chi^2 = 47.40$, 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 to 2.04; $p < 0.00001$; test for heterogeneity, $\chi^2 = 28.70$, df = 20, $p = 0.094$) and 1.74 (95% CI, 1.48 to 2.05; $p < 0.00001$; test for heterogeneity, $\chi^2 = 18.68$, 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 to 1.84; $p < 0.00001$; test for heterogeneity, $\chi^2 = 53.02$, 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 to 1.80; $p < 0.00001$; test for heterogeneity, $\chi^2 = 25.50$, df = 26, $p = 0.49$) and 1.78 (95% CI, 1.56 to 2.03; $p < 0.00001$; test for heterogeneity, $\chi^2 = 26.08$, df = 21, $p = 0.2$), respectively.

It is stated in the Cochrane Review[26] that three studies directly compared the effect of high-intensity versus low-intensity support (two studies with gum and one with patches). This direct comparison was not included in the Cochrane Review and was, therefore, not available for the present review.

One newly identified RCT[30] 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 3 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 5 (*Table 28*). 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 OR of 1.29 (95% CI, 0.66 to 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*. The results are presented graphically in appendix 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 for 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 of these factors, 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 were performed using either the gum or patches. There is clear evidence of statistical

TABLE 3 *The effect of clinical/recruitment setting on the effectiveness of NRT versus placebo or no treatment*

Type of NRT	Setting	Peto OR (95% CI)	*p* value for comparison	No. of studies in meta-analysis	χ^2 test for heterogeneity (df; *p*)
NRT gum	Community	1.67 (1.46 to 1.90)	< 0.00001	24	33.54 (23; 0.072)
	Smoking clinic	1.98 (1.56 to 2.52)	< 0.00001	7	5.81 (6; 0.45)
	Primary care	1.76 (1.50 to 2.07)	< 0.00001	18	13.80 (17; 0.68)
	Hospital	1.13 (0.84 to 1.51)	0.4	3	1.28 (2; 0.53)
NRT patch	Community	1.92 (1.67 to 2.22)	< 0.00001	20	28.33 (19; 0.077)
	Primary care	1.47 (1.18 to 1.83)	0.0005	6	8.38 (5; 0.14)
	Hospital*	1.74 (1.19 to 2.54)	0.004	4	2.09 (3; 0.55)
	Over the counter	1.96 (1.41 to 2.72)	0.00007	3	0.54 (2; 0.77)

* *Hospital inpatients or hospital outpatients. Does not include smokers attending smoking clinics based in hospitals or mixed populations of hospital patients and community volunteers*

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 subgroup 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 indicates that NRT is as effective in these subgroups 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 subgroup 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 versus 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 patches, 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 for community volunteers.

Comparison of NRT versus other interventions for smoking cessation

NRT versus other NRT or combinations of NRT. Several studies explored the effect of comparing different combinations of NRT versus NRT alone and were pooled within the Cochrane Review.[26] The data are presented graphically in appendix 11. The pooled OR for combination NRT versus monotherapy NRT was 1.55 (95% CI, 1.17 to 2.05; $p = 0.002$; test for heterogeneity, $\chi^2 = 7.93$, 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 to 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 to 1.43; $p = 0.2$).

In summary, 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.

NRT versus bupropion SR. One study comparing NRT directly with bupropion SR[41] was incorporated in the Cochrane Review.[26] 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.[33] It should be noted that these two studies are also discussed in the section on effectiveness of bupropion (see page 24). These studies were not pooled as there was significant clinical heterogeneity. *Table 4* presents the analysis from the Cochrane Review, which is based on the single double-blind study mentioned above.[41] 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.

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

NRT versus other active interventions. The Cochrane Review of NRT in smoking cessation did not include direct comparisons of NRT with other active interventions.[26] Three newly identified published RCTs were identified that compared NRT with a comparator other than placebo or no treatment.[27–29] Details of these studies are given in appendix 5 (*Table 28*).

Wong and co-workers[29] compared NRT patch with naltrexone (a long-acting opioid antagonist which blocks certain effects of drugs such as heroin and morphine) in a placebo-controlled RCT. They found that continued abstinence at 6 months was achieved in 28% of participants receiving the NRT patch, in 9% of participants receiving naltrexone only, in 27% of participants receiving the patch plus naltrexone, and in 8% receiving placebo alone. The Peto OR for the NRT patch versus naltrexone was 3.50 (95% CI, 1.72 to 7.14; $p = 0.0006$).

Clavel-Chapelon and co-workers[28] compared nicotine gum (2 mg *ad libitum*) with acupuncture and with the gum and acupuncture combined in a placebo-controlled RCT. Abstinence rates at the 12-month assessment were: placebo gum plus placebo acupuncture, 10.3% (95% CI, 7.1 to 14.7); placebo gum plus acupuncture, 6.5% (95% CI, 4.1 to 10.1); nicotine gum plus placebo acupuncture, 10.9% (95% CI, 7.4 to 15.9); and nicotine gum plus acupuncture, 11.2% (95% CI, 8.0 to 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 to 3.26; $p = 0.1$). At a 4-year assessment, abstinence rates were: placebo gum plus placebo acupuncture, 7.3% (95% CI, 4.5 to 11.6); placebo gum plus acupuncture, 5.1% (95% CI, 3.0 to 8.5); nicotine gum plus placebo acupuncture, 6.2% (95% CI, 3.2 to 11.8); and nicotine gum plus acupuncture, 6.1% (95% CI, 3.7 to 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 to 1.80; $p = 0.3$).

The RCT by Jensen and co-workers[27] compared silver acetate chewing gum with NRT gum and ordinary gum. Abstinence rates at the 6 months' assessment were: 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. The Peto OR calculated for NRT

TABLE 4 *Comparison between NRT patch and bupropion SR*

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

gum versus silver acetate was 0.75 (95% CI, 0.51 to 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,[28] while in the other study the placebo response was very high, but this study was unblinded.[27] 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 28,000 participants (this figure was estimated from the main comparisons included in the Cochrane Review[26]). 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. However, there are no data to indicate that other forms of NRT are less efficacious.

The data are much weaker for the comparison of 16 hour and 24 hour 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 were very difficult to investigate within 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).[26] 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. While 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 active intervention has been demonstrated to be comparable in effectiveness to NRT.

Bupropion SR

Two systematic reviews,[25,42] three newly identified published RCTs[47,49,53] and four newly identified unpublished trials[33,34,43,44] and three sets of additional unpublished data[44–46] for three published trials[47–49] were also identified. Where appropriate, the results from newly identified RCTs were combined with the studies included in the Cochrane Review.

Systematic reviews

Description of systematic reviews

One Cochrane Review[42] and one systematic review in the form of a US Public Health Service report[25] were identified. The US report included only articles published in peer-reviewed journals between 1 January 1975 and 1 January 1999, and therefore is less comprehensive and less up to date than the Cochrane Review. Thus, only the Cochrane Review[42] was used as a source of effectiveness data for bupropion SR in this report.

The Cochrane Review assessed the effectiveness of antidepressant medications in aiding long-term smoking cessation.[42] It included five trials with bupropion SR as the main intervention. Most of these trials are listed in appendix 12. The RCTs had 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.[48] In addition, only one study compared bupropion SR directly with NRT.[41]

Two studies included in the Cochrane Review evaluated bupropion SR 300 mg/day compared with placebo.[50,51] All participants also attended smoking cessation and relapse prevention meetings. A multicentre study evaluated bupropion SR in doses of 100 mg/day, 150 mg/day or 300 mg/day against placebo for 7 weeks.[52] The main publication for this study reported point prevalence abstinence rates.[52] Continuous abstinence rates at 12 months were provided by

Glaxo Wellcome. A second multicentre study compared a combined treatment of 300 mg bupropion SR plus the nicotine transdermal patch to bupropion SR alone, patch alone and placebo in a factorial design.[52] One study evaluated bupropion SR for relapse prevention in people who had quit during 7 weeks of open-label bupropion SR therapy.[48] In the treatment group, bupropion SR was provided for a further 45 weeks. In all the trials, included in the Cochrane Review, participants were not depressed at study entry, but may have had a past history of depression.[42]

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).[42] 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.[42] 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 was checked formally according to specified criteria, which were 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. Appropriate meta-analyses with a test for heterogeneity were performed and the results are presented in full.

Newly identified RCTs

Description of newly identified RCTs

Three newly identified published RCTs were identified.[47,49,53] In addition, four newly identified unpublished trials[33,34,43,44] and three sets of additional unpublished data[44–46] for three published trials[47–49] were also identified. All these studies included comparisons with placebo, except for one that compared bupropion SR with NRT gum (4 mg).[33] 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 8 (*Table 62*). One of the newly identified published studies randomised participants via a randomisation code (block randomisation) provided by the sponsoring company, although it was unclear whether intervention assignment was adequately concealed.[47] A second study randomised participants using a 1:1 ratio via a central code kept by the company, and concealment of allocation appeared adequate.[49] The other study did not report any details of the randomisation procedure.[53] All three studies stated the number of participants randomised, outlined the eligibility criteria and reported comparable groups at baseline. One study was underpowered[53] and no sample-size calculations were reported in one study.[47] The sample size of the third study[49] 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.[49] All three studies were reported as 'double-blind', although the success of blinding was not checked. Blinding may have been compromised in one study[49] because participants had received bupropion SR previously and, therefore, may have been able to detect whether they were receiving the active intervention or placebo. All studies clearly reported withdrawals. It was clear in two of the studies that an intention-to-treat analysis had been undertaken.[47,49] Continuous abstinence was defined as a self-report of no smoking and a carbon monoxide level less than 10 ppm in all three studies. In two studies[47,49] 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 US $100 for participating in the study.[53]

Details of the four newly identified, unpublished trials[33,34,43,44] cannot be discussed for reasons of commercial confidentiality.

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

All the results presented in this section were 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[47,49,53] are summarised below and presented in appendix 5 (*Table 29*).

The double-blind RCT by Tashkin and co-workers[47] included 404 participants, aged 35 years or older, with mild to moderate chronic obstructive pulmonary disease. Three-months abstinence rates were: 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 of 1.88 (95% CI, 1.02 to 3.48).

Gonzales and co-workers[49] conducted a multicentre, randomised, parallel-group, double-blind, placebo-controlled, 1-year study of participants who had previously failed to abstain from smoking while taking bupropion SR. At 6 months, abstinence rates in the bupropion SR and placebo groups were 12% (27/226) and 2% (5/224), respectively. In this study the response in the placebo group was particularly low, resulting in a large statistical difference between the active intervention and placebo groups 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.

The RCT by Hertzberg and co-workers[53] included 15 participants with a primary diagnosis (DSM-IV criteria) of post-traumatic stress disorder.[53] 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 the abstinence rates were 40% ($n = 4$) for bupropion SR and 20% ($n = 5$) for the placebo group.

The studies already included in the Cochrane Review were pooled with the newly identified published RCTs. Comparisons were made by 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*.

If the results presented in *Figure 1* are pooled using a random effects model the OR for bupropion SR versus placebo is 2.76 (95% CI, 1.67 to 4.56). Although the specific details of the unpublished trials cannot be presented in this

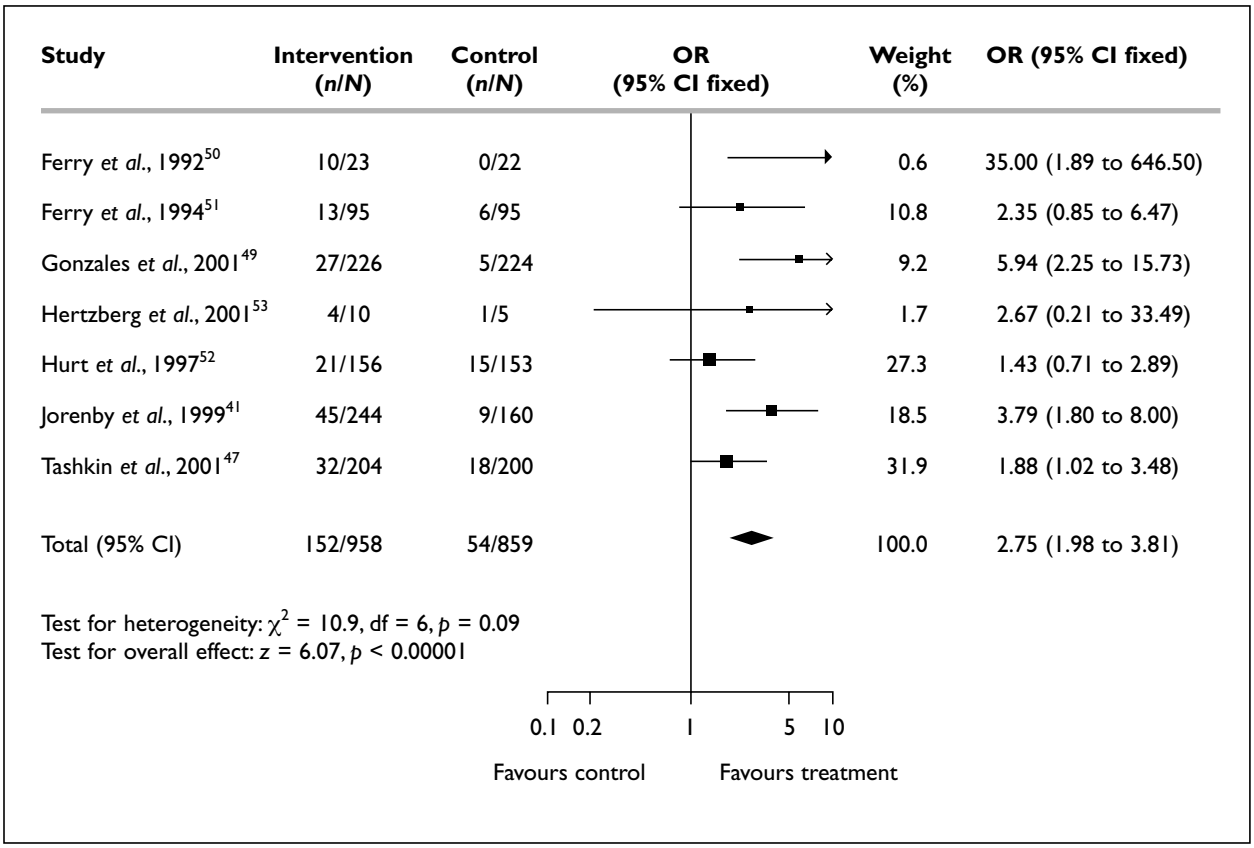

FIGURE 1 *Abstinence from smoking for bupropion SR versus placebo for 6 months and 12 months (combined) of smoking cessation: Forest plot with abstinence rates and pooled ORs (published data only)*

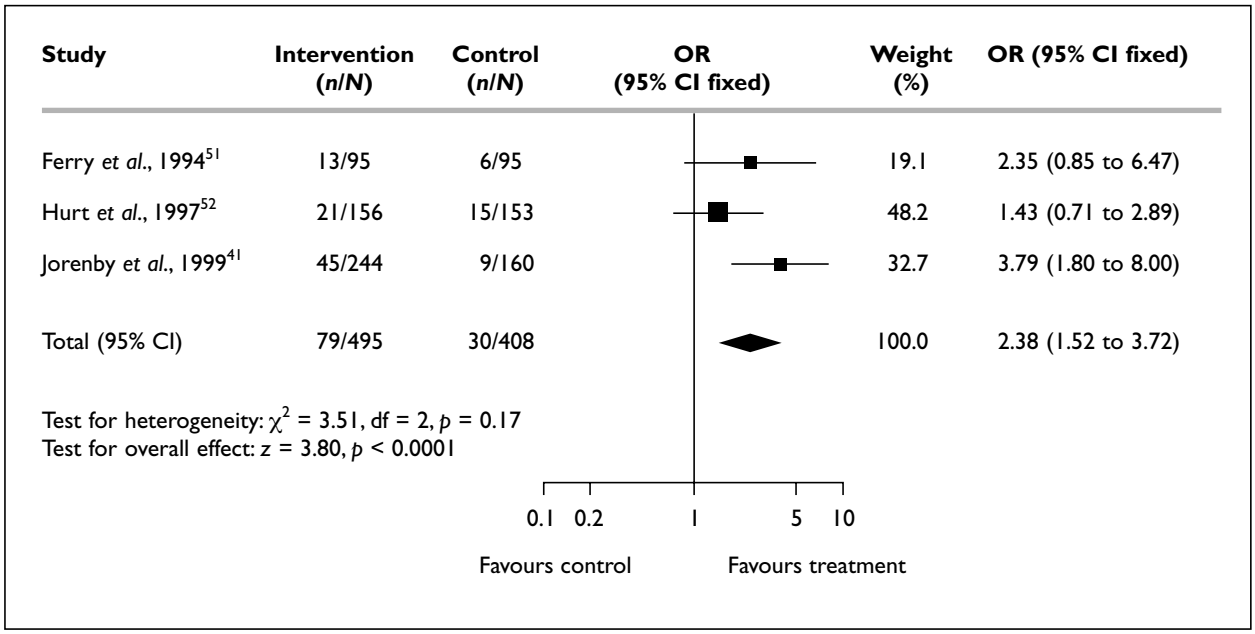

FIGURE 2 *Abstinence from smoking for bupropion SR versus placebo for 12 months smoking cessation: Forest plot with abstinence rates and pooled ORs (published data only)*

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 to 3.19) or, using a random effects model, OR = 2.45 (95% CI, 1.72 to 3.49).

If the results presented in *Figure 2* are pooled using a random effects model, the OR for bupropion SR versus placebo is 2.31 (95% CI, 1.25 to 4.28). If the unpublished studies are included, the result is OR = 2.21 (95% CI, 1.66 to 2.94) or, using a random effects model, OR = 2.20 (95% CI, 1.46 to 3.30).

The effectiveness of bupropion SR versus placebo in subgroup populations

The effectiveness of bupropion SR versus placebo was studied in the following subgroups:

- smokers with chronic obstructive pulmonary disease
- smokers with cardiovascular disease
- smokers who had failed to achieve abstinence with a previous course of bupropion SR.

The effectiveness of bupropion SR versus placebo in smoking cessation in **smokers with chronic obstructive pulmonary disease** was studied in a single RCT.[47] This study has been described above (see the description of the RCT by Tashkin and co-workers on page 22). The effectiveness of bupropion SR in this population was generally comparable to that in the general smoking population.

The effectiveness of bupropion SR in **smokers with established stable cardiovascular disease** has been investigated in one study, which is as yet unpublished.[34]

The effectiveness of bupropion SR in **smokers who had failed to achieve abstinence from smoking with a previous course of bupropion SR** was investigated in one study.[49] This study has been described previously (see page 22). 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 the effectiveness for bupropion SR versus placebo clearly indicate the effectiveness of bupropion SR. There is no real difference in the results whether all durations of follow-up are considered or just those of 12 months.

The evidence from a single study indicates that the effectiveness of bupropion SR in smokers with chronic obstructive pulmonary disease appears to be comparable with that in the general population of smokers at 6 months 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 rates achieved were lower.

Effect of clinical setting on effectiveness of bupropion SR
There was 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 have been conducted in clinics, with smokers recruited by advertisement.

Bupropion SR versus other active treatments
In clinical trials bupropion SR has been compared with NRT,[33,41] but not with any other active intervention for smoking cessation. One of the comparisons of bupropion SR with NRT has been published[41] and was included in the Cochrane Review.[42] 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.[33] It should be noted that these two studies are also discussed in the section on the effectiveness of NRT (see page 19).

Table 5 presents the analysis from the Cochrane Review, which is based on a single study.[41] 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 based on only 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 the 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 1 year after the end of therapy.[48]

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 population. There is evidence from a single study that bupropion SR is as effective in smokers with chronic obstructive pulmonary disease 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.

Adverse events and safety

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

Adverse events and safety of NRT

Two systematic reviews,[26,54] plus a total of 63 individual studies (for a breakdown of references by study design see *Table 6*) 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 the primary objective of which 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 5 *Comparison between NRT patch and bupropion SR*

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

TABLE 6 *Summary of the studies included in the review for adverse events and the safety of NRT*[*]

Design	Objective of or type of study					Total
	Incidence of adverse events	Investigating specific aspects of the safety profile	Pregnancy	Surveillance	Individual cases of adverse events	
RCT	*n* = 1[55]	*n* = 15[56–70]	*n* = 2[31,71]	–	–	*n* = 18[31,55–71]
Non-RCT	–	*n* = 3[72–74]	–	–	–	*n* = 3[72–74]
Uncontrolled	*n* = 7[75–81]	*n* = 10[82–91]	*n* = 2[92,93]	–	–	*n* = 19[75–93]
Case–control	*n* = 1[94]	–	–	–	–	*n* = 1[94]
Surveillance	–	–	–	*n* = 5[95–99]	–	*n* = 5[95–99]
Case reports or series	–	–	–	–	*n* = 17[100–116]	*n* = 17[100–116]
Total	*n* = 9[55,75–81,94]	*n* = 28[56–70,72–74,82–91]	*n* = 4[31,71,92,93]	*n* = 5[95–99]	*n* = 17[100–116]	*n* = 63[31,55–116]

[*] *Some studies have been published in additional references: Tzivoni and co-workers[66] also published as Tzivoni and co-workers,[117] Wallstrom and co-workers[83] also published as published as Wallstrom and co-workers,[118] Spyker and co-workers[95] also published as Spyker and co-workers[119] and Oncken and co-workers[71] also published as Hardardottir and co-workers[120]*

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.[26,54] One was a Cochrane Review (most recently updated July 2001)[26] and the other a meta-analysis of adverse events associated with NRT.[54] Details are given in appendix 6 (*Table 51*).

Quality of systematic reviews of NRT

The quality of the Cochrane Review[26] has been discussed previously in this report (see page 14). In terms of adverse event and safety data, the review 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[54] 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 December 1996. The validity of studies was not formally assessed, but 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[26] reported that the major side-effects associated with nicotine gum were hiccups, gastrointestinal disturbances, jaw pain, and orodental problems. 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; 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.[54] A total of 34 RCTs plus one study on contact sensitisation were included in this meta-analysis. Most of these studies are listed in appendix 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 is 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 events.

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

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.

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

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

A total of nine published studies where the primary objective was to investigate the incidence of adverse events with NRT were identified.[55,75–81,94] Of these, one was an RCT,[55] one was a case–control study,[94] and seven were uncontrolled studies,[75–81] one of which reported the adverse event data for a subset of what was originally an RCT.[79]

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

The quality assessment data are presented in full in appendix 8. The one RCT study[55] was of good quality, except for some lack of clarity in reporting withdrawals. Of the uncontrolled studies, it was unclear in four studies[75,77,78,80] if the sample size was appropriate; participant accountability was unclear in two studies;[76,77] statistical methods were not described or were unclear in four studies;[76,78–80] in one study the design was not appropriate;[75] and in another it was unclear if the measurements were appropriate.[80] 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 1 year.[79]

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

Details of the individual studies are presented in appendix 6. The types of NRT investigated were:

- NRT patch
- NRT nasal spray
- NRT gum.

NRT patch. There was one randomised, placebo-controlled, double-blind study.[55] 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 adverse events are summarised in *Table 8*.

The one case–control study to investigate a possible link between NRT patch use and occurrence of myocardial infarction[94] found that 3/653 in the intervention group had used NRT patch within the 7 days prior to their hospital admission for myocardial infarction (0.46% as compared with patch use in the controls (30/2990, 1%) (OR = 0.46; 95% CI, 0.09 to 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 myocardial infarction were statistically significantly more common in the those who

TABLE 7 *Adverse events associated with the use of the NRT patch*[54]

Adverse event	Proportion of participants reporting an adverse event		RR (95% CI) and homogeneity
	NRT patch	Placebo	
Myocardial infarction	3/36 (1%)	3/362 (1%)	Incidence of myocardial infarction low, possibly because people at risk would not be treated with NRT
Stroke	1/354 (0.3%)	2/357 (1%)	RR vs placebo 0.54 (0.02 to 6.73) Homogeneity (p = 0.38)
Tachycardia	2/239 (1%)	None reported	–
Palpitations	2/446 (0.4%)	8/451 (2%).	RR vs placebo 0.26 (0.04 to 1.10) Homogeneity (p = 0.54)
Angina	1/239 (0.4%)	1/238 (0.4%)	RR vs placebo1.00 (0.025 to 39.0)
Arrhythmia	11/406 (3%)	9/411 (2%)	RR vs placebo 1.26 (0.56 to 2.87) RR per 21 mg nicotine 1.43 (0.48 to 4.24) Homogeneity (p = 0.24)
Hypertension	8/354 (2%)	5/357 (1%)	RR vs placebo 1.60 (0.52 to 5.48) RR per 21 mg nicotine 1.79 (0.50 to 6.45) Homogeneity (p = 0.20) Reported in two 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 vs placebo 1.08 (0.75 to 1.55) RR per 21 mg nicotine 1.18 (0.87 to 1.59) Homogeneity (p = 0.25)
Unimproved ulcerative colitis	32/75 (43%)	Treatment 45/77 (58%)	RR vs placebo 0.73 (0.54 to 1.01) Homogeneity (p = 0.68) Reported in two 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 vs placebo 1.48 (0.71 to 3.07) RR per 21 mg nicotine 1.27 (0.91 to 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 vs placebo 1.91 (0.63 to 6.54) RR per 21 mg nicotine 2.12 (0.62 to 7.27) Reported in one trial
Respiratory symptoms other than asthma or bronchitis	23/892 (3%)	2/497 (0.4%)	RR vs placebo 5.68 (1.64 to 38.7) RR per 21 mg nicotine 5.96 (1.79 to 19.9) Homogeneity (p = 0.55)

continued

TABLE 7 contd *Adverse events associated with the use of the NRT patch*[54]

Adverse event	Proportion of participants reporting an adverse event		RR (95% CI) and homogeneity
	NRT patch	Placebo	
Urogenital symptoms	0/115 (0%)	1/199 (1%)	–
Neurological symptoms	4/115 (3%)	1/159 (1%)	RR vs placebo 3.80 (0.51 to 10.6) Homogeneity (p = 0.57) Reported in two trials
Localised skin irritation	884/3584 (25%)	410/3102 (13%)	Range of RR 1.10 to 5.57 Homogeneity (p = 0.011) Reported in 23 trials
Chest pain	11/1228 (1%)	7/1200 (1%)	RR vs placebo 1.52 (0.60 to 3.85) RR per 21 mg nicotine 2.02 (0.69 to 5.94) Homogeneity (p = 0.50)
Headache	264/2624 (10%)	206/2133 (10%)	RR vs placebo 1.06 (0.89 and 1.25) RR per 21 mg nicotine 1.02 (0.87 to 1.19) Homogeneity (p = 0.46)
Fatigue, malaise	8/414 (2%)	9/358 (3%)	RR vs placebo 0.63 (0.25 to 1.61) RR per 21 mg nicotine 0.93 (0.26 to 3.33) Homogeneity (p = 0.16)
Sweating	51/164 (31%)	46/164 (28%)	RR vs placebo 1.11 (0.81 to 1.52) RR per 21 mg nicotine 1.23 (0.80 to 1.90) Homogeneity (p = 0.095)
Dizziness	117/1599 (7%)	87/1104 (8%)	RR vs placebo 1.00 (0.78 to 1.28) RR per 21 mg nicotine 1.04 (0.72 to 1.48) Homogeneity (p = 0.38)
Sleep disturbance	280/1490 (19%)	117/1451 (8%)	RR vs placebo 2.31 (1.89 to 2.83) RR per 100 mg nicotine 2.03 (1.71 to 2.41) Homogeneity (p = 0.22)
Alteration in taste	27/1101 (2%)	16/1043 (2%)	RR vs placebo 1.55 (0.82 to 2.93) RR per 21 mg nicotine 1.24 (0.65 to 2.37) Homogeneity (p = 0.15)
Alteration in mood, mental status	85/382 (22%)	61/380 (16%)	RR vs placebo 1.39 (1.08 to 1.78) RR per 21 mg nicotine 1.55 (1.10 to 2.19) Homogeneity (p = 0.081)
Urticarial reaction	0/115 (0%)	1/119 (1%)	–
Unspecified adverse effects	106/822 (13%)	64/598 (11%)	RR vs placebo 1.24 (0.95 to 1.63) RR per 21 mg nicotine 1.29 (0.92 to 1.79) Homogeneity (p = 0.63)

RR, relative risk

TABLE 8 *Number of patients experiencing at least one serious adverse event with the NRT patch*

Adverse event	NRT patch		Placebo	
	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	–

received the NRT patch than in the controls. The analysis incorporated adjustment of confounders. The findings of this study suggest that use of the NRT does not precipitate myocardial infarction in these high-risk individuals.

A large uncontrolled follow-up study of 1481 adults investigated the adverse events associated with the 21 mg/24 hour patch.[76] The participants were adult smokers, with a mean age of 41 years (standard deviation (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; in 36 (2.6%) of the participants the reaction was a serious one. There was no association between pre-existing skin disorders and moderate–severe application site reactions (hazard ratio < 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%); and 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 4 weeks followed by NRT patch (22 mg) for a further 4 weeks.[75] 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%; and itching only, 7.5%. Difficulty in sleeping was reported by 13 (32.5%) participants in total. Nine (25%) participants reported experiencing vivid/unusual dreams during the 44 mg dose period, and one (2.5%) participant 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 8 weeks) as an aid to smoking cessation in adolescent smokers (mean ± SD age, 15.9 ± 1.3 years; range 13–17 years) who had been smoking for a mean of 2.6 years (SD = 1.6).[80] In this study, 59% of participants reported a skin reaction. Other adverse events were headaches (41%), nausea/vomiting (41%), dizziness (27%), tired-ness (27%) and arm pain (22%). None of these events were considered serious or life-threatening, and they did not lead to the discontinuation of patch therapy.

Confidential information regarding NRT patch (NiQuitin CQ) therapy was also available in the GlaxoSmithKine submission to the National Institute for Clinical Excellence.[99] This information cannot be included in this review for reasons of commercial confidentiality.

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

NRT nasal spray. Two small prospective uncontrolled studies of the NRT nasal spray were identified.[77,78] One study included 50 adult smokers, who were treated with nicotine nasal spray, 1–2 mg/h for only 7 days.[77] 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 in the nose, throat or unspecified area ($n = 14$), 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 (a 72-year-old female) suffered a stroke. 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 the use of the spray.

The other study of the nasal spray included only 40 adult smokers with a well-documented history of chronic rhinitis and/or chronic sinusitis.[78] Seventy-nine per cent 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 6.

In summary, the adverse events 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.

NRT gum. Two studies that investigated the safety of the NRT gum were identified.[79,81] One study reported mainly the effects on nicotine levels of chewing NRT gum.[81] The other study reported adverse event data for 925 participants who had entered the Lung Health Study, had been randomised to special intervention (which included NRT gum use), rather than usual care, and who had achieved abstinence.[79] In summary, neither of the studies relating to gum use is of good quality or particularly informative regarding the profile of adverse events. Further details are given in appendix 6.

Summary of findings from studies where the 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 the most common with the NRT nasal spray. No useful data were available from these studies regarding NRT gum or lozenge/sublingual tablet or NRT inhaler.

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. The studies addressed the effects of NRT on:

- cardiovascular function
- the blood lipid profile

TABLE 9 *Incidence of adverse events reported during a study of NRT nasal spray*[78]

Adverse event	Adverse events (%)		
	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

- the endocrine system
- the cutaneous inflammatory response
- endothelial dysfunction
- platelet activation
- glucose tolerance
- body weight change
- the oral mucosa.[56–70,72–74,82–91]

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,[58] one was unblinded[70] and for four studies the level of blinding was unclear.[62,63,67,121] Overall, the quality of the RCTs was limited: mainly in terms of accountability and analysis. Participant accountability was poor in seven studies[58,61,63,66,68–70] and in only two studies were the results clearly analysed using an intention-to-treat analysis.[56,67] Generally the quality of the uncontrolled studies appeared adequate, the main problem for many being an uncertainty regarding the sufficiency of the sample size.[83–85,89–91] 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

Effects of NRT on cardiovascular function.

A total of 16 studies that investigated the effect of NRT on cardiovascular function were identified.[56,57,59–62,64–66,72–74,86–89,117] (It should be noted that two references[66,117] refer to the same study). These studies included nine RCTs,[56,57,59–62,64–66,117] three non-RCTs[72–74] and four uncontrolled studies.[86–89]

Six of the RCTs included healthy individuals.[56,57,60,61,64,65] All except one[65] were placebo controlled and double blind, and investigated the effect of NRT on blood pressure. The number of participants in these studies ranged from ten to 50. Three studies used the NRT patch,[57,61,64] one used a nasal spray[56] and two used NRT gum.[60,65] Three of the studies were performed in smokers,[57,64,65] one in non-smokers,[56] one in a combination of smokers and non-smokers,[61] and one in users of smokeless tobacco.[60] In non-smokers NRT was shown to acutely increase systolic blood pressure and mean arterial blood pressure, but not diastolic blood pressure or heart rate.[56] In smokers, application of the NRT patch produced a moderate acute increase in mean arterial blood pressure, but over a period of 14 days had no effect on systolic blood pressure and may very slightly reduce diastolic blood pressure.[57,64,65] In smokeless tobacco users, use of nicotine gum had no effect on blood pressure or heart rate.[60] 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 carbon monoxide levels, heart rate, systolic blood pressure and diastolic blood pressure.

Two of these RCTs also examined the effect of NRT on cardiac conduction.[57,64] The largest (50 participants) and longest study (2 weeks treatment with 14 mg and 21 mg patches) reported no significant differences in electrocardiogram parameters, heart rate or blood pressure between treatment and placebo groups.[64] The other study, of a crossover design with 27 participants, reported that the RR interval appeared significantly reduced.[57] 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 NRT patches. This suggests that NRT patch treatment leads to an autonomic state intermediate between that observed during smoking and that observed during placebo-patch administration, reflecting only minor disturbances of autonomic cardiac control.

There were three RCTs in patients with cardiovascular disease.[59,62,66,117] Two were double-blind, placebo-controlled studies conducted in patients with coronary artery disease. The studies involved 77–106 participants.[59,66,117] The other RCT was a small, unblinded study in participants with suspected coronary artery disease.[62] 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,[59,66,117] found no effect of NRT patch use on resting heart rate, systolic blood pressure, diastolic blood pressure, signs of ischaemia on ambulatory electrocardiogram monitoring or nocturnal arrhythmia. One study reported fewer angina attacks.[59]

The third RCT[62] 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-RCTs[72–74] and the uncontrolled studies that investigated the cardiovascular effects of NRT are given in appendix 6.[86–89] The findings of these studies generally support those of the RCTs. However, as they are small studies and the reliability of their findings is limited, they are not discussed here in further detail.

In summary, overall the RCTs do not suggest any significant adverse cardiovascular effects of NRT in healthy adults, in terms of the effect on either blood pressure or conduction. There is also no evidence to suggest any short-term adverse effects of NRT in patients with coronary artery disease. 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.

Effects of NRT on the blood lipid profile. The effects of NRT on the blood lipid profile were investigated in two studies.[60,90] One was a randomised, double-blind placebo-controlled study that included 56 users of smokeless tobacco.[60] The other was an uncontrolled, open-label study of 27 ex-smokers.[90] After 5 or 8 weeks of treatment no changes were seen in total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol or triglycerides, in either study.

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

Effects of NRT on 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.[61] 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 catheterisation 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.[62] 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 use of the spray (found by analysis of variance, $p = 0.017$).[58] The authors concluded that nicotine alone causes acute endothelial dysfunction, but to a lesser extent than cigarettes.

In summary, the effects of NRT on endothelial dysfunction appear to reflect those of nicotine acquired through smoking.

Effects of NRT on glucose tolerance. The effects of NRT on glucose tolerance have been investigated in a crossover design, partially blinded, placebo-controlled RCT that included 12 participants with type II diabetes mellitus.[63] 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 II 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.

In summary, the effects of NRT on glucose tolerance appear to reflect those of smoking, but occur to a lesser extent.

Effects of NRT on the cutaneous inflammatory response. Adverse cutaneous reactions are an adverse effect generally associated with the transdermal patch form of NRT. They have been studied in three uncontrolled studies: one in healthy smokers,[68] one in smokers with known sensitivity[84] and one in non-smokers.[85]

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 h), when each patch was worn for 48 hours. The treatment period was 42 days.[68] 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 the percentage with moderately intense erythema ranged from 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 NRT patch (six were atopic by skin prick test),[84] 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 other reacted to all three concentrations and four others had equivocal reactions. Only one equivocal reaction was seen with nicotine sulphate. Five participants had a positive allergic reaction to nicotine base. One participant had a positive reaction only to nicotine sulphate, the patch matrix and 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 2 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 ($p < 0.003$).[85] 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 that nicotine delivered by patch transiently suppresses the cutaneous inflammatory response, but the clinical significance of the results is unclear.

In summary, the data from the studies that investigated the potential of the NRT patch to cause skin reactions are 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.

Effects 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.[83] Eight participants developed lesions on the floor of mouth. All these lesions occurred during weeks 1–6 and had healed by 6 months. Of those lesions from which a biopsy was taken ($n = 11$), 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.[118]

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

Effects of NRT on body weight change. One study investigating the effects of NRT on weight gain in association with smoking cessation was identified.[69] This was an 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, $n = 17$) eligible for this analysis at 1 year. For those participants receiving NRT gum (2 mg), the mean body mass index changed by 1.2 kg/m^2 relative to a baseline of 25.3 kg/m^2 (SD = 4.3 kg/m^2). For those receiving NRT gum (4 mg) the body mass index changed by 1.3 kg/m^2 relative to a baseline of 28.2 kg/m^2 (SD = 6.2 kg/m^2). In those on placebo the change was 1.2 kg/m^2 relative to a baseline of 26.7 kg/m^2 (SD = 5.7 kg/m^2). For those still using gum at 3 months the mean increase in body mass index was 1.8 kg/m^2 in those using placebo gum compared to approximately 0.5 kg/m^2 in those in the two active gum groups, but by 1 year the difference had been eroded.

In summary, 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 after 1 year there is no effect of NRT on body weight.

Studies that investigated the abuse potential of NRT. A total of four studies investigated the abuse potential of NRT.[67,70,82,91] Two were RCTs:[67,70] one of these was unblinded and gave no details regarding the method of allocation used[70] and the other was partially blinded.[67] One of the RCTs studied different types of NRT[70] and the other studied different methods of NRT withdrawal.[67] The remaining two studies were uncontrolled studies,[82,91] one being very small.[91]

The unblinded RCT included adult smokers in an investigation of the relative abuse potential of the different forms of NRT (gum, patch, spray, inhaler).[70] 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.

The second RCT[67] 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

TABLE 10 *Measure of abuse potential of NRT*[70]

Outcome measure	Gum (*n* = 127)	Patch (*n* = 124)	Spray (*n* = 126)	Inhaler (*n* = 127)
Amount of product used since last visit (week 15) (mean ± SD)	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) (mean ± SD)	5 ± 3.2	6.5 ± 3.8	4.6 ± 4.0	5.2 ± 4.0
Degree of dependence on the product (week 15) (%)	22	0	20	33
Proportion of participants still using NRT (week 15) (%)	7	2	10	7

starting. At the end of 6 weeks the proportion of participants who had not relapsed to gum or smoking was 67% (95% CI, 29.9 to 92.5) for the abrupt withdrawal group, 71.4% (95% CI, 29.1 to 96.3) for the taper with placebo gum group, and 60% (95% CI, 26.2 to 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 gum 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.[82,91] One study assessed the acute effects of NRT nasal spray or inhaler,[91] while the other assessed the long-term effects of NRT gum.[82] The acute study was small, including only 12 adult smokers who had been deprived of nicotine overnight prior to testing.[91] 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 NRT gum 2 mg for either 1 or 3 months.[82] There was evidence of withdrawal symptoms (i.e. difficulty in concentrating, increased variability in reaction-time tests, 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 1-month and 3-month treatment groups.

In summary, 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.

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 fetus. Women who smoke are already exposing themselves and the fetus 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.[31,71,92,93] One was a placebo-controlled RCT using NRT patches[31] and one was an acute, randomised, crossover comparison of NRT with smoking.[71] The other two studies were small uncontrolled studies.[92,93] All the studies investigated the effects of smoking compared with those of the NRT patch (21 mg). Further details are given in appendix 6.

The placebo-controlled RCT[31] 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. The mean birth weight was 3457 g in the nicotine group and 3271 g in the placebo group (mean difference 186 g (95% CI, 35 to 336). Among children born after 37 weeks' gestation the mean birth weights were 3539 g and 3381 g, respectively (mean difference 157 g (95% CI, 25 to 291)). The proportion of infants with weight under 2500 g 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. The rate of preterm delivery was 8% in the nicotine group and 10% in the placebo group (RR = 0.8 (95% CI, 0.4 to 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. These data cannot reliably inform about safety or otherwise of nicotine patches in pregnancy.

The acute RCT[71] found that the area under the curve for plasma nicotine during patch use was 93 ng-h/ml compared with 89 ng-h/ml while smoking ($p = 0.77$), but the measure of fetal hypoxia during patch use was not different from that while smoking. The acute effects of nicotine on the measure of fetal health are apparently similar regardless of the 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 fetal well-being.[92,93] The main finding in the larger of the two studies[92] was that during the 4 days of smoking abstinence and nicotine patch use, morning fetal 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 fetal well-being after placement of the NRT patch.

In summary, 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 fetus 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 of smoking, although generally these effects are reduced. There is no evidence that NRT-acquired nicotine has any greater effects than an individual would be exposed to while smoking.

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 to whom the drug is prescribed after it has been licensed 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 prelicensing clinical studies.

Description of surveillance studies of NRT

Three published reports of surveillance data for NRT were identified.[95,97,119] Two unpublished reports were also identified,[98,99] but for reasons of commercial confidentiality they were 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 as 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 US Food and Drug Administration Spontaneous Reporting System.[95,119] A total of 3848 adverse events (11.8 adverse events per million treated participants) were reported with the NRT patch and 1281 events (12.3 per million treated participants) with the gum. The data for specific adverse events are summarised in *Table 11*.

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 *Table 11,* 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 is the gum.

The UK Medicines Control Agency 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.[97] These include 13 fatalities

TABLE 11 *Adverse events reported to the US Food and Drug Administration Spontaneous Reporting System*[95]

Adverse event	NRT patch		NRT gum	
	No. of events reported	No. of events per million treated	No. of events reported	No. of events per million treated
Dermatological (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

(classified as seven cardiovascular, three cerebrovascular, one neurological, one congenital and one stillbirth). Non-fatal adverse events reported with NRT are: gastrointestinal (n = 139), cardiovascular (n = 79), abnormal dreams or nightmares (n = 60), musculoskeletal (n = 42), allergies (n = 16), cerebrovascular (n = 11) and congenital abnormalities (n = 8).

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).[96] Of these, a total of nine (five myocardial infarction, four chest pain) have been associated with NRT (eight with patches, one with gum). Nicotine was the second most frequently reported drug associated with myocardial infarction or chest pain. The proportion of drug-induced myocardial infarction 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.

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 (*Table 69*).

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 while 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 or case series were cardiovascular in nature or rashes with, or without, itchiness. No new areas of concern have been identified.

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, orodental problems **Patch**: skin sensitivity and irritation, respiratory symptoms other than asthma or bronchitis, sleep disturbances, alteration of mood **Inhaler**: throat irritation, coughing, oral burning **Nasal spray**: nasal irritation, runny nose **Nicotine sublingual tablets**: hiccups, burning and smarting sensation in the mouth, sore throat, coughing, dry lips, 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, 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 adverse events and serious adverse events **Gum**: addiction or dependence, oral problems, gastrointestinal, hiccups, withdrawal, no effect, headache **Patch**: dermatological (local or general), gastrointestinal, nausea, vomiting, hiccups, withdrawal, no effect, headache, nervous system, CNS, sleep and dream disturbance, dizziness
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 adverse events defined as serious**: fatalities (cardiovascular, cerebrovascular, neurological, congenital, stillbirth) **Non-fatal adverse events reported with NRT**: gastrointestinal, cardiovascular, abnormal dreams or nightmares, musculoskeletal, allergies, cerebrovascular, congenital abnormalities
General points	–	–	All classes of adverse event were 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 this table, there were 18 times more allergy-related events. Overall, the patch is eight times more likely to be associated with an adverse event than is gum
Comments on quality/validity	Limited information for one study;[26] one study[54] had limited searching	Generally limited quality, particularly for sample size, accountability and description of statistical methods	Good surveillance studies, but inherently of limited quality

continued

TABLE 12 contd *Summary of adverse events and safety data for NRT*

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 coronary artery disease
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 1 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 abuse potential
Use in pregnancy	There is only a very limited amount of information relating to the safety of NRT in pregnancy. There is no indication of a significant harmful effect to the fetus associated with NRT. However, of concern is the finding that NRT patch may deliver more nicotine than would be delivered by smoking

CNS, central nervous system

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,[13,42] and 60 individual studies (see *Table 13*) 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[99]), and 36 case reports or case series. Within the individual studies (irrespective of design) there were five where the primary objective was to investigate the incidence of adverse events, 14 studies that described investigations related to some specific aspect of the safety profile of bupropion, such as its effect

TABLE 13 *Summary of published references included for adverse events and safety of bupropion*[*]

Design	Objective of or type of study					Total
	Incidence of adverse events	Investigating specific aspects of the safety profile	Pregnancy	Surveillance	Individual cases of adverse events	
RCT	–	*n* = 7[122–128]	–	–	–	*n* = 7[122–128]
Non-RCT	–	*n* = 1[129]	–	–	–	*n* = 1[129]
Uncontrolled	*n* = 6[99,131–135]	*n* = 5[136–140]	–	–	–	*n* = 11[99,131–140]
Case–control	–	–	–	–	–	*n* = 0
Survey	–	*n* = 1[141]	–	–	–	*n* = 1[141]
Surveillance	–	–	–	*n* = 4[97,99,142,143]	–	*n* = 4[97,99,142,143]
Case reports or series	–	–	*n* = 1[144]	–	*n* = 35[145–179]	*n* = 36[144–179]
Total	*n* = 6[99,131–135]	*n* = 14[122–129, 136–140,141]	*n* = 1[144]	*n* = 4[97,99,142,143]	*n* = 35[145–179]	*n* = 60[97,99,122–129, 131–179]

[*] *van Wyck Fleet and co-workers[132] has also been published as Peck and co-workers.[181] Briggs and co-workers[144] is also included in Wisner and co-workers.[180] The study by GlaxoSmithKline[99] is a company submission not just a single study, and therefore may appear in more than one section*

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 surveillance study) are unpublished and are not discussed further.[99]

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.[13,42] 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.[42] 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 7 (*Table 61*).

Quality of systematic reviews of bupropion

The quality of the Cochrane Review has been discussed previously (see page 14).[42] In terms of adverse event and safety data the review summarises 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. The 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 the list in appendix 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; and 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, the incidence was 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 groups. In the second study the incidence was 8% in the bupropion SR (300 mg) group, 6% in the bupropion SR (100 mg) group and 5% in the bupropion SR (150 mg) group, compared with 5% in the placebo group. In the third study, in which participants received treatment for 1 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 in 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 150–300 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 RCTs 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.

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

Description of studies where the 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.[131,134,135] Two were uncontrolled cohort studies[134,135] and one was a small uncontrolled study.[131] In addition, two reports of data pooled from collections of clinical trials were identified.[132,133] It should be noted that the study by van Wyck Fleet and co-workers[132] is also published as Peck and co-workers.[181] One of these studies included all participants enrolled in the clinical trials programme of bupropion IR from 1970 to 1981, as reported by Wellcome Laboratories.[132] Another study included all participants known to have been treated with bupropion IR prior to its receiving marketing authorisation.[133] The clinical data included in this study were made available by Burroughs Wellcome, and included the total number of participants exposed to bupropion and all reports of seizure to the company (which the authors are confident includes all actual seizures).

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

Of the prospective studies,[131,134,135] 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[131,135] was appropriate, and in one study the sample size did not appear to be appropriate.[131] The validity of measures was unclear in two studies[11,135] and the suitability of the outcome measures was unclear in one study.[134] Patient accountability was unclear in one study[134] and the statistical methods were not clearly described in a further two studies.[131,135] The two reports of retrospective pooling of data[132,133] 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 studies the statistical methods used appeared suitable.

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

Of the three prospective uncontrolled studies,[131,134,135] one study was small, including only 22 participants, and was therefore of extremely limited utility in determining the safety of bupropion.[131] Further details are given in appendix 7.

A multicentre, unblinded, uncontrolled study investigated the adverse events associated with 8 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.[135] 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 8-week treatment phase and a further five during a continuation of treatment. The calculated observed seizure rate during the 56 days of the treatment phase was 0.24% (upper one-sided 95% CI, 0.38%). The observed seizure rate for the whole study was 0.40% (upper one-sided 95% CI, 0.58%). The survival analysis performed on participants who took 300–450 mg/day (n = 2708) showed a cumulative rate of 0.36% (upper one-sided 95% CI, 0.57%) in the 56-day treatment period.

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 were reported as follows: psychiatric (n = 56), unrelated to drug (e.g. hospitalisation for road traffic accident) (n = 22), and possibly bupropion IR related (drug discontinued) (n = 6).

A second multicentre, unblinded, uncontrolled study investigated the adverse events associated with bupropion SR.[134] This study utilised bupropion SR (titrated from 50 to 150 mg twice daily) for a period of 8 weeks, which could then be extended for up to 1 year, and included a total

of 3100 adult patients with a DSM-III-R diagnosis of depression. A total of 2057 (66%) patients completed the 8-week acute phase and 1577 (77%) of these entered the continuation phase.

Three participants experienced a seizure; two within the first 8 weeks, giving an observed incidence rate of 0.06% (upper one-sided 95% CI, 0.14%). The observed seizure rate for the whole study period (1 year) was 0.10% (upper one-sided 95% CI, 0.19%). In participants who consumed a therapeutic dose of bupropion SR (n = 2958) the survival analysis yielded a cumulative seizure rate of 0.08% (upper one-sided 95% 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 11 years 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 of the 3100 participants reported 54 serious adverse events. These included suicide attempt or overdose (nine participants), accidental injury (four participants) and myocardial infarction (three participants, all of whom 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 to be 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.[132] All participants had demonstrated normal and/or clinically acceptable values for physical examinations, vital signs, clinical laboratory tests (haematology, clinical chemistry, urinalysis) and electroencephalogram. Concomitant medication, with the exception of chloral hydrate, had been prohibited, except in three studies where antipsychotics were also permitted. The duration of treatment was 4–13 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	Patients withdrawing due to adverse events (%)
Excitement/agitation	9.1
Anticholinergic	5.4
Miscellaneous	4.6
Motor disturbance	4.5
Psychological problems	3.9
Dermatological	3.0
Nausea/vomiting	2.7
Drowsiness	2.6
Weight loss	2.4
Headache/nasal congestion	2.4
Thinking difficulties	2.1

[*] *Participants may have withdrawn due to more than one event. Only adverse events with an at least > 2% occurrence are included, but figures of 1.8% and 1.4% are given in the table*

Although the majority of participants had no change in the electroencephalogram 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 2 or 4 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/day 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.[133] 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.[132] A total of 37/4262 of subjects 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 seizures occurred ranged from 100 mg to 9000 mg. The length of time for which 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 subjects being on that dose for 15 days or less. For the 21 subjects 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 regard 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 the database (n = 1153 participants), the cut-off of 2% for inclusion in this summary must mean that many events were not included in this publication.

The seizure rate from the retrospective study is much higher than that from the 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 where the primary objective was to investigate the incidence of adverse events with bupropion

For bupropion SR the common adverse events 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, dermatological, nausea/vomiting, drowsiness, weight loss, headache/nasal congestion, thinking difficulties, dizziness and tachycardia/palpitations.

The calculated observed seizure rate with bupropion IR during a 56-day treatment phase was 0.24% (upper one-sided 95% CI, 0.38%). The observed seizure rate for the whole study duration was 0.40% (upper one-sided 95% CI, 0.58%) compared with 0.06% (upper one-sided 95% CI, 0.14%) for a period of 956 days and 0.10% (upper one-sided 95% CI, 0.19%) for 1 year with bupropion SR. In addition to seizures, other adverse events that were life-threatening or required hospitalisation with bupropion SR were psychiatric or unrelated to the drug (e.g. hospitalisation for a road traffic accident). Serious adverse events included suicide attempt or overdose, accidental injury, myocardial infarction (all had pre-existing cardiovascular pathology) and six deaths.

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 addressed specific investigations conducted in relation to the adverse events and safety profile of bupropion, concentrating on the possible cardiovascular effects of bupropion, its possible effects on sexual function and its effect on weight.[122–128,130,136–141] It should be noted that all studies relating to bupropion-associated seizures have been included in the previous section.

Three of the seven RCTs were double-blind,[122,123,126] two were unblinded[124,125] and for two studies the status of blinding was unclear.[127,128] One study failed to achieve at least 80% completion,[126] one was unclear regarding the number of patients withdrawn[128] and three studies were unclear in both these respects.[122,123,125] 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.[136,137,140] Two studies described the statistical methods poorly[136,137] and for two studies the appropriateness of the statistical methods was unclear.[137,140] In two studies the appropriateness of the study design was unclear.[137,138] One study[141] was a small survey, with all the inherent unreliability of such a study.

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

Effects of bupropion on cardiovascular function. A total of six studies that examined the possible effects of bupropion on cardiovascular function were identified.[122–124,129,136,137] Three of these studies were RCTs,[122–124] one was a non-RCT[129] and two were uncontrolled studies.[136,137] 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, none of whom had a cardiovascular disorder.[122,123] The third RCT was a very small (ten participants), unblinded, crossover comparison in patients with a history of congestive heart failure.[124]

In the two RCTs in participants without cardiovascular disease,[122,123] no effects on sinus heart rate or cardiac conduction were reported. Neither study reported symptomatic orthostatic hypotension. However, in one study[122] 8/55 patients had orthostatic changes (defined as a drop of 20 mmHg after 1 minute standing), which was at least 20 mmHg greater than the orthostatic drop at baseline. In the small RCT of patients with chronic heart failure,[124] 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 mmHg.

The non-RCT, in which 23 patients were treated with bupropion IR 300–750 mg/day, reported no significant changes in any of the electrocardiographic parameters measured.[129] The two uncontrolled studies[136,137] also found no evidence of adverse cardiovascular effects of bupropion IR. Further details are given in appendix 7.

In summary, 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 or cardiovascular function.

Effects of bupropion on sexual function. A total of seven studies were identified that investigated the effects of bupropion on sexual function.[125–128,139–141] Four of these studies were RCTs: three were conducted in patients suffering from depression[125,126,128] and one in healthy volunteers.[127] Of the non-RCTs, two were uncontrolled studies[139,140] and one was a survey.[141] Two of these studies were conducted in patients suffering from depression[139,141] and one in non-depressed men with diabetes.[141] Further details of all the following studies are given in appendix 7 (*Tables 53*, *57* and *59*).

Two of the RCTs were double-blind, parallel-group studies that compared bupropion SR with sertraline (an antidepressant drug).[125,126] 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 2 weeks of therapy with bupropion SR conducted in 13 healthy volunteers.[127] 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.[139] 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 21–60 years, with erectile dysfunction due to their diabetes.[139] There was no evidence from this study that bupropion IR worsened or interfered with sexual desire or erectile function.

A survey of psychiatric outpatients from a single clinic found that of 22 patients who were receiving bupropion IR, none reported decreases in sexual function over baseline.[141] In contrast, some patients reported significant increases in sexual function over baseline, in terms of libido, arousal, and duration and intensity of orgasm, whereas those receiving other antidepressants (fluoxetine, paroxetine or sertraline) reported detrimental effects in terms of sexual function. The very small sample size severely limits the reliability of these findings.

In summary, the data from the RCTs indicates that bupropion is less likely to cause sexual dysfunction than are other antidepressants. The one very small RCT in healthy volunteers indicates no adverse sexual effects of bupropion SR, a finding that is 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.

Effect of bupropion on body weight change. One small uncontrolled study was identified that investigated the effect of bupropion IR on body weight.[138] A total of 58 outpatients diagnosed with a non-psychotic depressive disorder, who poorly tolerated tricyclic antidepressants (many specifically due to weight gain), were treated with bupropion IR 50–600 mg/day (most common dose 300–450 mg/day) for up to 1 year (mean 9 months). After 3, 6, 9 or 12 months on bupropion IR therapy (mean 9 months) the mean terminal

weight change was 4.8l lb for men and 8.0 lb for women. Overall, 42 patients (72%) lost weight (35 patients lost more than 5 lb) and 24% gained weight (seven patients gained more than 5 lb), with 4% showing no change. Changes in weight corresponded poorly to patients' reports of appetite suppression or increase. This was a small study, with limited details of participants, and would have been better conducted as an RCT. The applicability of these findings to participants using bupropion SR for smoking cessation is questionable.

Studies related to the use of bupropion during pregnancy or lactation. Preclinical data have not established the safety of bupropion in pregnancy (Summary of Product Characteristics for Zyban)[18] 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 is related to just a single individual.[180] 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 corresponding infant serum levels were < 5 ng/ml, < 20 ng/ml, and < 20 ng/ml, respectively. 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 or cardiovascular function. The data from RCTs indicates that bupropion is less likely to cause sexual dysfunction than are other antidepressants. The one very small RCT in healthy volunteers indicates no adverse sexual effects of bupropion SR, a finding that is 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 the aid of bupropion SR do not gain weight. There is no evidence to support the removal of the contraindication to bupropion SR in pregnancy or breast-feeding.

Surveillance studies of bupropion

The reason for including this type of study has been discussed previously (see pages 8 and 9).

Description of surveillance studies of bupropion
Three published sources of surveillance data relating to bupropion SR were identified.[97,142,143] All three studies report data from country-specific safety monitoring databases: the Medicines Control Agency,[97] Australian Adverse Drug Reaction Advisory Committee[142] and the Canadian Adverse Drug Reaction Monitoring Program.[143]

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 the publication of reports of adverse drug reactions, with the larger databases publishing only information on the adverse events most commonly reported to them. All 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 that may affect the findings.

Adverse events data from surveillance studies of bupropion
The published data are summarised in *Table 15*. 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, paraesthesia, Stephens–Johnson syndrome, maculopapular rash, skin discoloration, fever, aggravated Bell's palsy, asthenia, sensation of warmth, cold extremities, peripheral oedema, mouth oedema, pharynx oedema, aggressive reaction, anorexia, paranoia, confusion, depression, nervousness, impaired concentration, agitation, flushing, myocardial infarction, angina pectoris, dyspepsia, hyperventilation, rhinitis, arthralgia, arthropathy, myalgia, mydriasis, photophobia, earache and 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 the publication of reports of adverse drug reactions, with the larger databases publishing only information on the adverse events most commonly reported to them. The most commonly reported adverse events are: urticaria, insomnia, rashes, headache, dizziness, nausea, angioedema, tremor, depression,

TABLE 15 *Number of adverse reactions reported for bupropion SR (Zyban)*

Adverse event	Medicines Control Agency	Adverse Drug Reactions Advisory Committee	Canadian Adverse Drug Reactions 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 18 August 1998 to 1 December 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
Angioedema	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

[*] *Approximately half the participants had either a past history of seizures and/or risk factors for their occurrence. The estimated incidence of dose-related risk of seizure was 0.1% (1/1000)*
[†] *Classed as convulsions/twitching*
[‡] *One case of convulsions only*
[¶] *The sum of the reports exceeds the total number*
[§] *In nine cases, participants were not taking bupropion at the time of death*
[**] *The Adverse Drug Reactions Advisory Committee is satisfied, to date, that bupropion has not emerged as a cause of unexpected deaths*
[#] *Stevens–Johnson syndrome*

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 and dysaesthesia.

Case reports and case series of bupropion

Description of case reports and case series of bupropion

Thirty-six case reports were included.[144–179] All except one,[144] 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.

Quality of case reports and case series of bupropion

Not applicable.

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

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 or 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, dyskinesia 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 while taking bupropion. Other adverse events reported include tinnitus, eosinophilia, transient ischaemic attack, 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 the psychiatric adverse effects of bupropion. Reports of serum-sickness-like reactions and rhabdomyolysis suggest possible areas for future vigilance.

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

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

TABLE 16 *Summary of the adverse events and safety data for bupropion SR and IR*

	Systematic reviews	Studies of incidence	Surveillance studies
Common adverse events	Rash, pruritus, irritability, insomnia, dry mouth, headache; tremor, urticaria	**Bupropion SR**: data on common adverse events leading to withdrawal are unpublished **Bupropion IR**: common adverse events leading to withdrawal were excitement/agitation, anticholinergic, miscellaneous, motor disturbance, psychological problems, dermatological, 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 differentiation between adverse events and serious adverse events Urticaria, insomnia, rashes, headache, dizziness, nausea, angioedema, 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 the drug (e.g. hospitalisation for road traffic accident), possibly bupropion related (drug discontinued). Serious adverse events included: suicide attempt or overdose, accidental injury, myocardial infarction (all who had pre-existing cardiovascular pathology), six deaths	–
Seizures	Crude rate of 0.3% at 6 days with bupropion IR and 0.06% with bupropion SR	Calculated observed seizure rate with bupropion IR during the 56-day treatment phase was 0.24% (upper one-sided 95% CI, 0.38%). The observed seizure rate for the whole study duration was 0.40% (upper one-sided 95% CI, 0.58%) compared with 0.06% (upper one-sided 95% CI, 0.14%) for 956 days and 0.10% (upper one-sided 95% CI, 0.19%) for 1 year with SR	118 from a base of 390,000 individuals exposed from 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 study.[42] The other study was of good quality, except for a lack of individual study details[13]	Generally of limited quality, particularly relating to limited reporting of adverse events other than seizures	Good-quality surveillance studies

continued

***TABLE 16* contd** *Summary of the adverse events and safety data for bupropion SR and IR*

Safety issues	
Cardiovascular	The available studies indicate that bupropion does not have any clinically significant adverse effects on cardiac or cardiovascular function
Sexual dysfunction	The data from RCTs indicates that bupropion is less likely to cause sexual dysfunction than are other antidepressants. The one very small RCT in healthy volunteers indicates no adverse sexual effects of bupropion SR; a finding that is 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 weight	Very limited evidence that smokers abstaining with the aid of bupropion SR do not gain weight
Pregnancy	Contraindicated

Chapter 5

Economic evaluation of smoking-cessation interventions

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

Review of existing studies

Identified studies of the economic evaluation of smoking-cessation interventions are presented in appendix 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[23,182–186]
- several studies conducted in other countries that evaluated the cost-effectiveness of NRT are considered relevant[187–190]
- two studies carried out a cost–benefit analysis of bupropion SR for smoking cessation[191,192]
- some studies of smoking-cessation interventions provided useful information but did not estimate the cost-effectiveness of NRT or bupropion SR separately[193–195]
- one study, done in the USA, assessed the impact of insurance coverage on the use of smoking-cessation interventions.[196]

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

Estimating effectiveness in economic evaluation

The evaluation of the effectiveness of smoking-cessation interventions generally involves two stages (*Figure 3*):

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

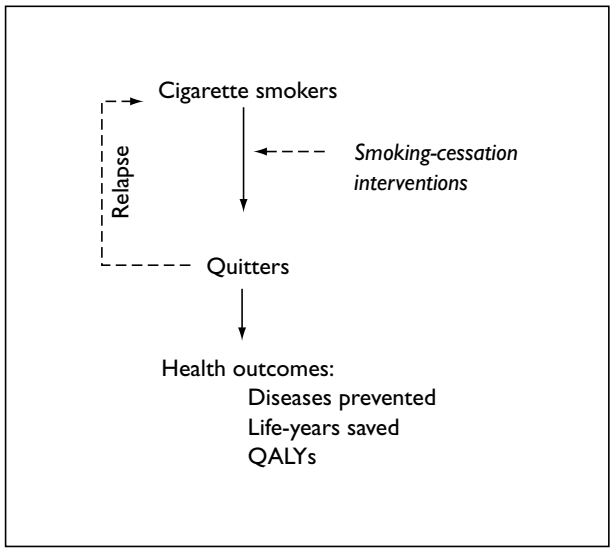

FIGURE 3 *The two-stage process for estimating the effectiveness of smoking-cessation interventions*

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 the 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 continuous abstinence for 6–12 months. Since in clinical trials the duration of follow-up is generally up to 12 months, 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 ranged from 0% to 50% (see appendix 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 when estimating the net effect of smoking-cessation interventions. In the existing economic evaluations, this ranged from 1% (most of the UK studies) to 8% per year. In one study,[186] it was 1.5% (95% CI, 1.2 to 1.8%) based on data from the Office of National Statistics' General Household Survey in the UK.

Side-effects due to smoking-cessation interventions were not incorporated in the existing economic evaluations. The assumption that there are no important side-effects associated with smoking-cessation interventions 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.

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 QALYs 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 is the numbers of quitters. The incremental life-years saved after cessation depends on many factors, such as the age and gender of the quitters, the number of cigarettes smoked, the 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[197] to estimate the impact of changes in smoking behaviour on specific diseases (lung cancer, coronary heart disease, chronic obstructive pulmonary disease) (see appendix 10). In other studies, the difference in the total mortality between smokers and non-smokers or former smokers was used to estimate the life-years saved after smoking cessation. For example, studies have used data from the cohort study of male doctors in England, conducted by Doll and co-workers,[198] or data from the 25-state Cancer Prevention Study done by the American Cancer Society.[199]

According to the existing studies of economic evaluation, the average life-years saved per quitter range from 0.28[183] to 2.4,[184] depending on the model and discount rate used. Parrott and co-workers,[23] using the PREVENT model and an annual discount rate of 1.5%, calculated the number of life-years saved per quitter to be about one. 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 estimated the number of life-years saved per long-term quitter as 1.31 for men aged 25–29 years, 0.47 for men aged 65–69 years, 1.43 for women aged 25–29 years and 1.41 for women aged 65–69 years.[187] The weighted average of life-years saved per quitter was 1.46. This study used a relapse rate of 45% and the quitters were 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, HECOS, has adopted an approach similar to the PREVENT model to estimate the life-years saved after smoking cessation.[185] 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.[185] In the HECOS model the duration of follow-up is up to 20 years, although the 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 (e.g. the PREVENT or HECOS models)

than in those based on comparisons of total mortality between smokers and quitters. For example, the PREVENT model compares deaths due to three smoking-related diseases (lung cancer, coronary heart disease, chronic obstructive pulmonary disease) between continued smokers and quitters. The average number of life-years saved per quitter calculated using the PREVENT model is 1.54 without discounting, and 0.99 using an annual discount rate of 1.5%.[23] In a study of male doctors (GPs) in England, Doll and co-workers used the total mortality of smokers and quitters to the estimated number of life-years saved per lifetime quitter (*Table 17*).[198,200] The study showed larger differences in life-expectancy between cigarette smokers and quitters, based on a 40-year follow-up. 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 (John Stapleton, personal communication).

TABLE 17 *The estimated number of life-years saved per lifetime quitter**

Age at which stopped smoking (years)	No. of life-years saved	
	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

* *Based on the total mortality of smokers and quitters; from the study by Doll and co-workers of male doctors in England*[198,200]

However, when using a model to estimate the number of life-years saved per quitter for the whole population, the generalisability of the results obtained by Doll and co-workers must be questioned. For example, quitters in that study had smoked about 10% less cigarettes per day than the continued smokers of the same age.[200] The cigarettes consumed by the smokers were unfiltered, and these may be more harmful than filtered cigarettes.[186] In addition, it is impossible to exclude the impacts of other socio-economic factors on the differences in mortality between the quitters and the continued smokers in the study.

An assessment of the results from the range of studies (see appendix 10) and consideration of the results obtained by Doll and co-workers suggests that a figure of 1.0–3.0 life-years saved per long-term quitter seems reasonable.

QALYs saved

A more important outcome is the number of QALYs saved after quitting cigarette smoking. However, this quantity is more problematic to calculate than life-years saved. 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.[188]

In the USA, Fiscella and Franks[188] estimated the number of QALYs saved after smoking cessation, using the results from the Healthy People 2000 Years of Healthy Life research project.[199] They calculated that the number of QALYs associated with a quitter was, on average, about 1.98 (range 0.69–2.38). In this study the quitters were 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 and co-workers[187] 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 quality of life due to quitting).

Estimating costs of smoking-cessation interventions

The viewpoint for analysis

The viewpoint for analysis has generally been that of the payers in the existing economic evaluation of smoking-cessation interventions (see appendix 10). A few studies have also provided results from the viewpoint of society or employers (who may be payers of healthcare insurance in the USA). In the UK studies the viewpoint for analysis is either the NHS and/or society,[23] the NHS [183–185] or the payers.[186]

Direct costs of smoking-cessation interventions

In studies that have adopted the viewpoint of payers, the costs associated with 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 1 year). Future costs, particularly costs averted

by health services because treatment of disease is avoided, were not included in most studies. The justification for excluding future averted healthcare costs is that there is uncertainty as to whether the reduced costs to the health services are offset 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 such costs, given the long time before they would accrue.

Empirical evidence indicates that smokers who fail to quit after a week of smoking-cessation intervention are unlikely to abstain despite continued treatment.[201–203] Thus, one study adopted an abstinence-contingent treatment model.[185] In this model, physicians continue giving pharmacological treatment only to those who abstain at each point of follow-up. The model may reduce the cost without there being an 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 long-term medical expenditure. One study suggests that smoking cessation may reduce the healthcare costs in the short term but would increase the healthcare costs eventually.[204] This conclusion has been disputed in several published letters.[205–209] It should be noted that discounting reduces the present value of the costs of long-term medical expenditure, and so these costs are unlikely to have much impact on estimates of cost-effectiveness.

The long-term economic outcomes of smoking have been estimated using the HECOS model.[185] It has been 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 was not considered in most of the studies in this review because of lack of accurate data and great uncertainty. The principal objective of healthcare interventions, it has been argued, should be to produce health gains such as a healthier population with a longer life-expectancy.[210]

Cost-effectiveness of smoking-cessation interventions

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

Cost per quitter

The cost per quitter is easiest of the values to estimate, and is useful when comparing different smoking-cessation interventions. In a UK study it was estimated that the average cost per quitter is £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).[23] In the study using the HECOS model, the average cost per quitter was £92 for advice only, £649 for pharmacological therapy and £1148 for group therapy (UK £, 1999).[185]

Higher costs per quitter are derived from monitoring the new smoking-cessation services set up in health action zones in England during the year April 1999 to March 2000.[211] 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 health action zones have been established by the government in England 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 was £5,026,000, including the costs of staff (£2,070,000), training (£268,000), advertising and 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 over-the-counter NRT was not included. The average cost per quit attempt (with a quit date) was £344 (i.e. £5,026,000/14,598), which is higher than that in many other economic evaluations. This may be due to there being a different definition of smoking-cessation attempts and due to the infrastructure required to implement the programmes.

Cost per life-year saved

The cost per life-year saved after smoking cessation ranges from less than £200 to more than £4500, according to several UK studies (see appendix 10). Parrott and co-workers reported that the average cost (UK £, 1997) per life-year saved is £174 for brief advice, £221 for advice plus self-help material, £269 for advice plus self-help material plus NRT, and £255 for special smoking-cessation clinics, from a viewpoint of the NHS.[23] In the study done using the HECOS model, the average cost per life-year saved was £1212 (UK £, 1999).[185]

In a major US study,[187] the average cost (US $, 1996) per life-year saved was $1496–5423 for counselling without NRT, $1581–3248 for counselling plus NRT patch, and $2461–6135 for counselling plus NRT gum (from the payer's viewpoint).

Cost per QALY saved

Two US studies have estimated the cost per QALYs saved as US $4546–10,943[187] and US $1108–4542.[187]

Incremental cost-effectiveness of NRT and/or bupropion SR

Several studies have reported the incremental cost of NRT per life-year saved. Parrott and co-workers[23] estimated the incremental cost per life-year saved to be £660 (from the NHS perspective). In three other studies, where NRT was provided in addition to advice, the incremental cost per extra life-year saved was estimated to be £4526 (UK £, 1992)[182] for patch and £1527 for nasal spray (UK £, 1993)[181] or £345–785 for NRT patch (UK £, 1998).[186]

In three different studies the incremental cost per life-year saved by adding NRT to counselling was found to be $4140–8421 (US $, 1984),[189] $4546–10,943 (US $, 1995)[188] and $1822–3686.[190]

Commentary

Dealing with uncertainty

Sensitivity analysis has been used in most of the existing studies of economic evaluation of smoking-cessation interventions. In the study by Fiscella and Franks,[188] Monte Carlo simulation was also used.

In a UK study by Stapleton and co-workers,[202] the incremental cost-effectiveness of GP advice plus NRT patch was shown to be sensitive to the quit rate, the cost of the NRT patch, life-years saved by stopping smoking and the relapse rate after 12 months of abstinence. In the studies by Fiscella and Franks[188] and Cromwell and co-workers,[187] the results were shown to be sensitive to the discount rate used for life-years saved

Overall, the results of the sensitivity analyses in the 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 and co-workers[212] 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). As the intensity of smoking-cessation interventions increases, both the cost and the effectiveness increase, but the cost increases more rapidly. For example, Parrott and co-workers[23] estimated the incremental cost per life-year saved to be £174 for brief advice only. The incremental cost per life-year saved by adding self-help material to GP advice was £362. On adding NRT to GP advice and self-help material, the incremental cost increased 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 (ICER) of more resource-intensive interventions still compared favourably with many accepted healthcare interventions. The incremental cost per life-year saved by smoking-cessation interventions is in the range US $1822–10,943. According to Tengs and co-workers,[213] the median medical intervention cost is $19,000 per life-year saved.

Generalisability

There may be questions about whether the results of trials can be generalised to the wider population. A further issue is the possible changes in cost-effectiveness as programmes expand. In the early stages 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.[210] The infrastructure costs of programmes may also need to be taken into account.

In a study by Buck and Morgan,[214] 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 intervention 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.

Remarks about existing economic evaluation studies

- Irrespective of the methods used or the assumptions involved, the results of existing

economic evaluations consistently suggest that smoking-cessation interventions are relatively cost-effective in terms of the cost per life-year saved.
- Adding NRT to the current practice is cost-effective, with a relatively low (under £1000) incremental cost per quitter. No published study has evaluated the relative cost-effectiveness of bupropion SR for smoking cessation.
- Based on results from trials, the additional number of quitters can be estimated by adding NRT or bupropion SR to advice or counselling. It is then simple to estimate the incremental years of life saved according to the ratio of life-years/quitters from existing studies. (This is the purpose of the modelling reported in the following section)
- 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 is been applied (i.e. the worst-case scenarios still provide estimates of cost-effectiveness better than many other medical interventions).

Decision analysis modelling

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

The model compares four smoking-cessation interventions (*Figure 4*):

- advice or counselling only (including GP advice and more intensive counselling by other health professionals)
- advice plus NRT
- advice plus bupropion SR
- advice plus NRT and bupropion SR.

The advice or counselling only option is considered as the reference (control) for estimating the 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 between the options modelled).

Estimating effectiveness

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

Relative effect of NRT and bupropion SR

In published studies, ORs have often been used to estimate the relative efficacy of NRT or bupropion SR for smoking cessation. Where possible, the estimates of ORs have been based on the results of meta-analyses of RCTs.[26,42,215] In the Cochrane Review, which includes more than 90 RCTs of NRT, the overall OR for abstinence with NRT versus control was 1.73 (95% CI, 1.62 to 1.85).[26] By including only the 70 RCTs with data for

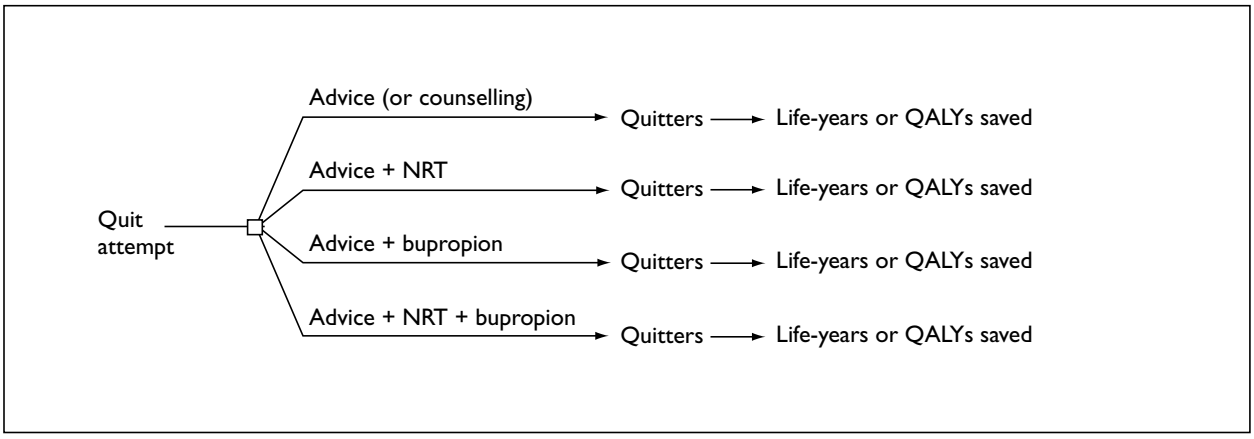

FIGURE 4 *Model structure for estimating the cost-effectiveness of smoking-cessation interventions*

12 months or more continued abstinence, the OR with NRT versus control is 1.67 (95% CI, 1.55 to 1.80).

In the Cochrane Review of the use of antidepressants for smoking cessation, pooling of the results from four trials yields an overall OR of 2.73 (95% CI, 1.90 to 3.94) with bupropion SR versus placebo.[42] When unpublished data are included, the relative efficacy of bupropion SR is smaller, the overall OR for bupropion SR versus placebo becoming 2.1 (95% CI, 1.62 to 2.73) for continuous abstinence at 12 months.

Only one trial has evaluated the combination of bupropion SR and NRT for smoking cessation.[41] The direct comparison of bupropion SR plus NRT versus placebo yields an OR of 3.0 (95% CI, 1.8 to 4.9). In the same trial, the quit rate in the bupropion SR plus NRT group was higher than that in the bupropion SR group, but the difference was not statistically significant. The OR with bupropion SR plus NRT versus bupropion SR alone is 1.26 (95% CI, 0.85 to 1.88). Using the adjusted indirect methods,[216,217] it could be estimated that the adjusted OR with bupropion SR plus NRT versus placebo is 2.65 (95% CI, 1.65 to 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[41] 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 for advice or counselling only, based on data from the published economic evaluations[23,185] 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% for advice only and 9% for counselling only. The quit rate of NRT and bupropion SR can then be estimated, using the OR and the quit rate in the control (advice or counselling only) group, as:

$$p_1 = \mathrm{OR} \times p_2 / (1 - p_2 + \mathrm{OR} \times p_2)$$

where p_1 is the quit rate with NRT, bupropion SR or NRT plus bupropion SR, and p_2 is the quit rate in the advice or counselling only group.

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 OR, the absolute difference in quit rate with NRT or bupropion SR depends on the quit rate in the control (advice or counselling only) group (*Table 18*). For example, an OR of 1.67

TABLE 18 *Estimating the 12-month quit rate for NRT or bupropion SR based on the OR (point estimates and 95% CIs) and quit rate in the control group*

	Point estimate	Low 95% CI	High 95% CI	Point estimate	Low 95% CI	High 95% CI
NRT vs control						
Control quit rate	0.0400	0.0400	0.0400	0.1000	0.1000	0.1000
OR	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 vs control						
Control quit rate	0.0400	0.0400	0.0400	0.1000	0.1000	0.1000
OR	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 + bupropion SR vs control						
Control quit rate	0.0400	0.0400	0.0400	0.1000	0.1000	0.1000
OR	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

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 OR of 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 plus advice and the advice-only group, and 5.7% (i.e. 15.7% – 10.0%) between the NRT plus counselling and the counselling-only group. The lifetime relapse rate is assumed to be 40% (range 30–50%).

Life-years saved and QALYs saved

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

Based on the ratio of 1.35 (QALYs/life-years saved) given in Fiscella and Franks[188] study, the number of QALYs per lifetime quitter is assumed to be, on average, 2.7 (range 1.35–4.05).

Estimating the cost of interventions

Estimates of the 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. As only the short-term cost is included in the model, costs are not discounted. The detailed assumptions are presented in *Table 19,* and further explanation is given below.

Brief advice from a GP

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 3 minutes to deal with smoking cessation and a further 3 minutes if a prescription is involved. Given that this consultation is taking place anyway, marginal costs apply. These were estimated by Netten and co-workers as £0.49 per minute.[218] Thus, for brief advice alone the costs would be £1.47 without prescription, and £2.94 if a 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 and co-workers[218] 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, and 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 that 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 their attempt at cessation. Judging from the results obtained by Jorenby and co-workers,[41] around half of patients in counselling might have ceased to attend and hence not collect the second 4-week prescription. The incidence of this occurrence is likely to be somewhat higher in patients who receive brief advice only.

NRT comes in a variety of formulations, each of which has a somewhat different length of application, which in turn will affect costs. An average 4-week cost is £37, and in the cheapest scenario all participants use NRT for 4 weeks, and one-third return for a further 4-week course. In the most expensive scenario, all participants use NRT for 4 weeks, two-thirds return for a further 4-week course, and half for a third 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- to 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 the same as practice nurses.

Main results of cost-effectiveness modelling

Cost per quitter

Baseline estimates of the cost per quitter for different interventions, obtained using average values under various assumptions, are presented in *Table 20.* Using brief advice without pharmacological treatment as the standard intervention, the average cost per lifetime quitter is £196 for

TABLE 19 *Estimated costs of smoking-cessation interventions*

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

TABLE 20 *Baseline estimates of the cost-effectiveness of smoking-cessation interventions*

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

ICER, cost (£) per lifetime quitter; ICER1, using the brief advice only or counselling only as the reference; ICER2, using the brief advice plus NRT or counselling plus NRT as the reference; ICER3, using the brief advice plus bupropion SR or counselling plus bupropion SR as the reference

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 cost per lifetime quitter is £2001 for counselling plus NRT, £1278 for counselling plus bupropion SR, and £1781 for counselling plus NRT and bupropion SR.

The results of sensitivity analyses, using the most unfavourable estimates of effect and the most expensive scenario for cost are presented in *Table 21*. The most pessimistic estimates of the incremental cost 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 QALY saved

The costs per life-year saved and per QALY saved, 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), are presented in *Tables 22* and *23*, respectively. According to the baseline estimates, the incremental cost per life-year saved is about £1000–2399 for NRT, £639–1492 for bupropion SR and £890–1969 for NRT plus bupropion SR.

Using the low estimates of effect and high estimates of cost, the most pessimistic result for the cost per life-year saved is £8413 for NRT, £7347 for bupropion SR and £13,612 for NRT plus bupropion SR.

According to the baseline estimates, the incremental cost per QALY saved is about £741–1777 for NRT, £473–1106 for bupropion SR and £660–1459 for NRT plus bupropion SR. The most pessimistic estimates of the cost per QALY saved are £6231 for NRT, £5442 for bupropion SR and £10,083 for NRT plus bupropion SR.

Impact on cost and effectiveness

The impact of NRT and bupropion SR on cost and effectiveness for the NHS in England and Wales was estimated using the results of the modelling and population data.[219] The total number of adults aged 16 years 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. If 30% of smokers were to use NHS smoking-cessation services, the total number of quit attempts would be 3.4 million.

Table 24 presents the impact of smoking-cessation interventions, assuming that only one strategy is available. The incremental estimate is perhaps most useful, and is also relatively accurate.

TABLE 21 *Sensitivity analyses: average and incremental costs (£) per lifetime quitter for different smoking-cessation interventions*

Assumptions	Ratio	Advice only	Advice + NRT	Advice + bupropion SR	Advice + NRT + bupropion SR
Low-effect model 1	ACER	235	2,978	2,860	5,301
Advice quit rate = 0.03	ICER1	–	6,954	6,254	11,554
Average estimates of costs	ICER2	–	–	464	38,006
Lower estimates of effect	ICER3	–	–	–	123,327
Low-effect model 2	ACER	783	1,506	1,455	2,367
Advice quit rate = 0.09	ICER1	–	2,893	2,606	4,963
Average estimates of costs	ICER2	–	–	207	17,103
Lower estimates of effect	ICER3	–	–	–	56,525
High-costs model 1	ACER	310	2,808	2,147	3,187
Advice quit rate = 0.03	ICER1	–	5,805	3,507	4,641
High estimates of costs	ICER2	–	–	Dominate	3,795
Average estimates of effect	ICER3	–	–	–	7,070
High-costs model 2	ACER	928	1,482	1,195	1,600
Advice quit rate = 0.09	ICER1	–	2,365	1,463	2,072
High estimates of costs	ICER2	–	–	Dominate	1,839
Average estimates of effect	ICER3	–	–	–	3,489
Low-effect and high-costs model 1	ACER	372	3,655	3,414	6,297
Advice quit rate = 0.03	ICER1	–	8,413	7,347	13,612
High estimates of costs	ICER2	–	–	Dominate	43,511
Lower estimates of effect	ICER3	–	–	–	145,764
Low-effect and high-costs model 2	ACER	1,114	1,904	1,803	2,880
Advice quit rate = 0.09	ICER1	–	3,419	2,984	5,774
High estimates of costs	ICER2	–	–	Dominate	19,580
Lower estimates of effect	ICER3	–	–	–	66,808

ACER, average cost-effectiveness ratio; Dominate, bupropion SR dominates NRT

TABLE 22 *Costs (£) per life-year saved: baseline estimates and according to different values of life-years saved per quitter*

	2.0 LYS per quitter		1.0 LYS per quitter		3.0 LYS per quitter	
	Average	Incremental	Average	Incremental	Average	Incremental
Standard reference: brief advice						
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
Standard reference: counselling						
Counselling alone	326	–	653	–	218	–
Counselling + NRT	586	1000	1173	2001	391	667
Counselling + bupropion SR	482	639	964	1278	321	426
Counselling + NRT + bupropion SR	657	890	1314	1780	438	594

LYS, life-year(s) saved

TABLE 23 *Costs per QALY saved: baseline estimates and according to different number of QALYs per quitter*

	2.7 QALYs per quitter		1.35 QALYs per quitter		4.05 QALYs per quitter	
	Average	**Incremental**	**Average**	**Incremental**	**Average**	**Incremental**
Standard reference: brief advice						
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
Standard reference: counselling						
Counselling alone	242	–	484	–	161	–
Counselling + NRT	434	741	869	1482	290	494
Counselling + bupropion SR	357	473	714	947	238	316
Counselling + NRT + bupropion SR	487	660	973	1319	324	440

TABLE 24 *Estimated impact of smoking-cessation interventions in England and Wales*[*]

	Total No. of attempts	Total cost (£ million)	Incremental cost (£ million)	Total No. of lifetime quitters	Incremental No. of quitters
Brief advice only	3,381,426	11.94	–	61,000	–
Brief advice + NRT	3,381,426	255.30	243.36	112,000	51,000
Brief advice + bupropion SR	3,381,426	257.26	245.32	143,000	82,000
Brief advice + NRT + bupropion SR	3,381,426	486.62	474.68	181,000	121,000
Counselling only	3,381,426	119.20	–	183,000	–
Counselling + NRT	3,381,426	348.56	229.36	297,000	115,000
Counselling + bupropion SR	3,381,426	350.52	231.32	364,000	181,000
Counselling + NRT + bupropion SR	3,381,426	579.88	460.69	441,000	259,000

[*] *Assumptions: only one strategy is available; 30% of smokers will use NHS smoking-cessation interventions; baseline estimates as in* Table 25

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 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 plus NRT, 10% for advice plus bupropion SR, and 5% for advice plus NRT plus bupropion SR (*Table 25*). The total cost to the NHS is then £202 million, the total number of attempts to quit is about 3.4 million and the total number of lifetime quitters is about 135,000. Thus, the average cost per motivated-to-stop smoker and per lifetime quitter is about £59.6 and £1500, respectively.

If the percentage of smokers who use NHS smoking-cessation services is 10% and if 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 weeks is £344 and £870, respectively, as determined from the health action zones (see page XX).[2110] The high costs may be mainly due to the

TABLE 25 *Estimated impact of smoking-cessation interventions in England and Wales, assuming that motivated-to-stop smokers are distributed between the different strategies*[*]

	Proportion of smokers attempting to quit (%)	Distribution between advice and counselling	Distribution between smoking-cessation interventions	Total No. of users of interventions	Costs (£ million)	Quitters
Brief advice only	30	0.8	0.35	946,799	3.34	28,400
Brief advice + NRT	30	0.8	0.50	135,2570	102.12	74,390
Brief advice + bupropion SR	30	0.8	0.10	270,514	20.58	19,070
Brief advice + NRT + bupropion SR	30	0.8	0.05	135,257	19.46	12,090
Counselling only	30	0.2	0.35	236,700	8.34	21,300
Counselling + NRT	30	0.2	0.50	338,143	34.86	38,890
Counselling + bupropion SR	30	0.2	0.10	67,629	7.01	8,830
Counselling + NRT + bupropion SR	30	0.2	0.05	33,814	5.80	5,050
Total	–	–	–	3,381,426	201.52	208,030

[*] *Estimates are based on the results using baseline assumptions given in* Table 20

infrastructure required to implement the programmes, which does not appear to have been fully costed in the model. In a sensitivity analysis, assuming that 20% of motivated-to-stop smokers use smoking-cessation clinics and an average cost of £344 per attempt, the total cost will be £78 million to £233 million. If the total cost for other 80% of GP advice users remains the same (£48.5 million to £145.5 million), the total cost of smoking-cessation interventions to the NHS will be £126.5 million to £378.1 million.

Summary of cost-effectiveness modelling

- The results of the decision analysis modelling are similar to those reported in 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-year saved is about £1000–2399 for NRT, £639–1492 for bupropion SR and £890–1969 for NRT plus bupropion SR.
- The estimated cost of the smoking-cessation programme to the NHS in England and Wales would be about £67 million to £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 £500–1500).
- According to the available evidence, the incremental cost-effectiveness of bupropion SR is generally better than that of NRT. However, this conclusion should be interpreted cautiously because of very limited data on the relative efficacy and possible side-effects of bupropion SR.

Chapter 6
Discussion

Main effectiveness results

Effectiveness of NRT

The effectiveness of NRT has been investigated in a large number of, mostly placebo-controlled, studies. The data demonstrate the effectiveness of NRT compared with placebo or no treatment in smoking cessation. Although the majority of studies were performed using NRT gum or NRT patches, there are sufficient data on other forms of NRT to indicate that no difference in the levels of effectiveness is 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 heterogeneity 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 being 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 the effectiveness of NRT overall.

The evidence supporting any differences in the level of effectiveness within subgroups of smokers is weak. Such differences are not to be expected, as there is no real basis to suspect that 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, changes in participants' circumstances).

No analysis of self-referred patients versus physician-referred patients was 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 and non-motivated smokers was also impossible. 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 a 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 combinations of different NRT types is probably best determined by adverse effects rather than by 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, 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 while 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.

Effectiveness of bupropion SR

The number of studies of bupropion SR in smoking cessation is relatively small. However,

the studies are mainly of high quality and the level of evidence is good. There is clear evidence that bupropion SR is more effective than placebo, and no indication that bupropion SR is less effective in smokers with chronic obstructive pulmonary disease. 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 while using bupropion SR. There is no information to compare physician-referred and self-referred smokers, or motivated and 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.

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.

Main adverse effects and safety results

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.

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 9 weeks (or multiples thereof). 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) 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, 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 bupropion SR does appear to be better than that of bupropion IR.

As was already recognised, this review 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. Postmarketing safety monitoring demonstrates a significant level of seizures occurring in individuals treated with bupropion SR. This is possibly related to inappropriate prescribing or to inadequately strict screening for seizure potential. Significantly, no RCT of bupropion SR in smoking cessation 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).

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 healthcare interventions.

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

The results of this decision analytic modelling are broadly similar to those obtained in previous studies. The smoking-cessation interventions using NRT and/or bupropion SR are cost-effective compared with many accepted healthcare interventions. According to our estimates, the incremental cost per life-year saved is about £1000–2300 for NRT, £640–1500 for bupropion SR and £900–2000 for NRT plus bupropion SR. Our analysis extends the previous literature by comparing bupropion SR with NRT, showing that the former has a lower ICER 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 between 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 estimates of the cost per life-year saved and QALY saved are based on many assumptions covering quitters' or smokers' lifetimes, and hence are subject to great uncertainty. In particular, the effectiveness of smoking-cessation interventions may have been overestimated because the model does not consider the impact of possible changes in the 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 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 obtained 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 healthcare 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 that of 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 the data available on NRT. The use of conservative estimates of the effectiveness of bupropion SR cannot completely exclude the possibility that the relative efficacy of bupropion SR for smoking cessation has been overestimated. More importantly, use of bupropion SR needs more supervision by health professionals because of the rare but potentially serious side-effects. The possible costs and health consequences due to the side-effects of bupropion SR were not considered in the modelling.

Assumptions, limitations and uncertainties

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

Need for further research

The data on the clinical 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 studies would include a level of motivational support that was the maximum that could realistically be provided within the provision for smoking cessation.

Assuming that 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 smokers in a motivated to quit state until smoking cessation has been achieved?

Chapter 7

Conclusions

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

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Competing interests of expert panel

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Contributions of the authors

The contributions of the individual authors of the report are acknowledged. Nerys Woolacott (Research Fellow) was the lead reviewer responsible for writing the protocol and final review. She played a primary role in the selection of studies, and was involved in the extraction and quality assessment of the studies and the synthesis of the data.

Lisa Jones (Research fellow) assisted in the selection, data extraction/checking and quality assessment of studies. She also assisted in analysing and checking the data, and commented on and assisted with writing the draft report.

Carol Forbes (Research Fellow) assisted in the selection, data extraction/checking and quality assessment of studies. She also commented on and assisted with writing the draft report.

Lisa Mather (Information Officer) devised the search strategy and carried out literature searches. She wrote the search methodology sections of the protocol and report, and managed the interlibrary loans and the endnote library.

Amanda Sowden (Associate Director) was the review manager, responsible for the overall management of the project. She assisted in the preparation of the protocol and provided advice and comments on the final review

Fujian Song (Senior Research Fellow) developed the economic evaluation section of the protocol. He played a primary role in searching for and assessing published studies, the modelling of cost-effectiveness, and writing the section on cost-effectiveness of smoking cessation interventions.

James Rafferty (Health Economist) assisted in the development of the protocol, the assessment of published studies of economic evaluation and the modelling of cost-effectiveness. He also commented on the draft.

Paul Aveyard (Lecturer in Public health) contributed to the development of the protocol. He assisted in searching for and assessing published studies of economic evaluation, the modelling of cost-effectiveness, and estimating the costs of different strategies. He also commented on the draft.

Chris Hyde (Senior Lecturer) assisted in the development of the protocol, searching for and assessing published studies of economic evaluation, and the modelling of cost-effectiveness. He also commented on the draft.

Pelham Barton (Lecturer in Modelling) assisted with the modelling of cost-effectiveness of smoking cessation interventions and commented on the draft.

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References

1. NHS Centre for Reviews and Dissemination. Smoking cessation: what the health service can do. *Effectiveness Matters* 1998;**3**(1):1–4.
2. Brown RA, Larkin JC, Davis RL. Current concepts in the management of smoking cessation: a review. *Am J Management Care* 2000;**6**(3):394–404.
3. Pisinger C, Wennike P, Tonnesen P. Nicotine replacement therapy in patients with coronary heart disease. *CNS Drugs* 1999;**12**(2):99–110.
4. Haustein KO. Pharmacotherapy of nicotine dependence. *Int J Clin Pharmacol Ther* 2000;**38**(6):273–90.
5. Office for National Statistics. Living in Britain: results from the 1998 General Household Survey. London: The Stationery Office, 2000.
6. Skaar KL, Tsoh JY, McClure JB, Cinciripini PM, Friedman K, Wetter DW, *et al.* Smoking cessation: 1. An overview of research. *Behav Med* 1997;**23**(1):5–13.
7. Cinciripini PM, McClure JB. Smoking cessation – recent developments in behavioral and pharmacologic interventions. *Oncology* 1998;**12**(2):249–56.
8. Thompson GH, Hunter DA. Nicotine replacement therapy. *Ann Pharmacother* 1998;**32**(10):1067–75.
9. Gourlay SG, Benowitz NL. The benefits of stopping smoking and the role of nicotine replacement therapy in older patients. *Drugs Aging* 1996;**9**(1):8–23.
10. Drug and alcohol dependency. *MIMS* 2000; Dec:354–6.
11. McNeill A, Armstrong M. The impact of amfebutamone (bupropion) on National Health Service smoking cessation services. *Pharmaceut J* 2000;**265**(7125):860–2.
12. Drugs in substance dependence. *BNF* 2000; 4 Sep:244–5.
13. Holm KJ, Spencer CM. Bupropion – a review of its use in the management of smoking cessation. *Drugs* 2000;**59**(4):1007–24.
14. Lancaster T, Stead LF. Mecamylamine (a nicotine antagonist) for smoking cessation (Cochrane Review). In: The Cochrane Library Issue 4. Oxford: Update Software; 2000.
15. Benowitz NL, Peng MW. Non-nicotine pharmacotherapy for smoking cessation: mechanisms and prospects. *CNS Drugs* 2000;**13**(4):265–85.
16. Ferry LH. Non-nicotine pharmacotherapy for smoking cessation. *Primary Care; Clin Office Pract* 1999;**26**(3):653–69.
17. MTRAC. Summary Sheet for: Bupropion SR (Zyban). 2000.
18. GlaxoSmithKline. Zyban: summary of product characteristics. 2001. URL: http://corp.gsk.com/products/prescriptionmedicines.shtml
19. NHS Centre for Reviews and Dissemination. Manual for selecting reviews and writing abstracts for the Database of Abstracts of Reviews of Effectiveness (DARE). York: NHS Centre for Reviews and Dissemination, University of York; 16 Oct 2000.
20. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.
21. Crombie I. The pocket guide to critical appraisal: a handbook for healthcare professionals. 1st ed. London: BMJ Publishing Group; 1996.
22. Drummond M, O'Brien BJ, Studdard GL, Torrance GW, editors. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford Medical Publications; 1997.
23. Parrott S, Godfrey C, Raw M, West R, McNeill A. Guidance for commissioners on the cost effectiveness of smoking cessation interventions. *Thorax* 1998;**53**(Suppl 5 Pt 2):S1–38.
24. Health and Economic Consequences of Smoking model (HECOS). URL: http://www.ea3.lewin.com/hecos/whoweb.asp
25. Fiore MC, Bailey WC, Cohen SJ, *et al.* Treating tobacco use and dependence. A clinical practice guideline. Rockville, MD: US Department of Health and Human Services; 2000. Report No.: AHRQ publication No. 00-0032.
26. Silagy C, Mant D, Fowler G, Lancaster T. Nicotine replacement therapy for smoking cessation (Cochrane Review). In: The Cochrane Library Issue 3. Oxford: Update Software; 2001.
27. Jensen EJ, Schmidt E, Pedersen B, Dahl R. The effect of nicotine, silver acetate, and placebo chewing gum on the cessation of smoking. The influence of smoking type and nicotine dependence. *Int J Addict* 1991;**26**(11):1223–31.

28. Clavel-Chapelon F, Paoletti C, Benhamou S. Smoking cessation rates 4 years after treatment by nicotine gum and acupuncture. *Prev Med* 1997;**26**(1):28.

29. Wong GY, Wolter TD, Croghan GA, Croghan IT, Offord KP, Hurt RD. A randomized trial of naltrexone for smoking cessation. *Addiction* 1999;**94**(8):1227–37.

30. Solomon LJ, Scharoun GM, Flynn BS, Secker Walker RH, Sepinwall D. Free nicotine patches plus proactive telephone peer support to help low-income women stop smoking. *Prev Med* 2000;**31**(1):68–74.

31. Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstet Gynecol* 2000;**96**(6):967–71.

32. GlaxoSmithKline. Study number C-94-052-01. Evaluation of the efficacy and safety of Nicoderm. Data on file; 2000. Uxbridge: GlaxoSmithKline.

33. GlaxoSmithKline. Study number AK1A4008. Data on file; 1999. Uxbridge: GlaxoSmithKline.

34. GlaxoSmithKline. Protocol number ZYB40014. Data on file; 2000. Uxbridge: GlaxoSmithKline.

35. Perng RP, Hsieh WC, Chen YM, Lu CC, Chiang SJ. Randomized, double-blind, placebo-controlled study of transdermal nicotine patch for smoking cessation. *J Formos Med Assoc* 1998;**97**(8):547–51.

36. Tonnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. *Eur Respir J* 2000;**16**(4):717–22.

37. Joseph AM. Nicotine replacement therapy for cardiac patients. *Am J Health Behav* 1996;**20**(5):261–9.

38. Research Committee of the British Thoracic Society. Comparison of four methods of smoking withdrawal in patients with smoking related diseases. Report by a subcommittee of the Research Committee of the British Thoracic Society. *BMJ* 1983;**286**:595–7.

39. Campbell IA, Prescott RJ, Tjeder-Burton SM. Smoking cessation in hospital patients given repeated advice plus nicotine or placebo chewing gum. *Respir Med* 1991;**85**:155–7.

40. Mori T, Shimao T, Yulchiro G, Namiki M, Hyachi T. A clinical trial of nicotine chewing gum for smoking cessation [abstract 428]. In: 8th World Conference on Tobacco or Health; 30 March–3 April 1992; Buenos Aires, Argentina.

41. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;**340**(9):685–91.

42. Hughes JR, Stead, LF, Lancaster T. Antidepressants for smoking cessation (Cochrane Review). In: The Cochrane Library Issue 4. Oxford: Update Software; 2000.

43. GlaxoSmithKline. Protocol number ZYB40017. Data on file; 1999. Uxbridge: GlaxoSmithKline.

44. GlaxoSmithKline. Protocol number AK1406. Data on file; 1999. Uxbridge: GlaxoSmithKline.

45. GlaxoSmithKline. Protocol number ZYB40003. Data on file. Uxbridge: GlaxoSmithKline.

46. GlaxoSmithKline. Protocol number AK1A4013. Data on file; 2000. Uxbridge: GlaxoSmithKline.

47. Tashkin DP, Kanner R, Bailey W, *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; **357**:1571–5.

48. Hays JT, Hurt RD, Wolter TD. Bupropion SR for relapse prevention (Study 406). Poster presentation. In: Sixth Annual Conference of the Society for Research on Nicotine and Tobacco; 18–20 Feb 2000; Arlington, Virginia, USA.

49. Gonzales DH, Nides MA, Ferry LH, Kustra RP, Jamerson BD, Segall N, *et al.* Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001;**69**(6):438–44.

50. Ferry LH, Robbins AS, Scariarti PD, Masterson A, Abbey DE, Burchette RJ, *et al.* Enhancement of smoking cessation using the antidepressant bupropion hydrochloride [abstract 2670]. *Circulation* 1992;**86**(4 Suppl 1):671.

51. Ferry LH, Burchette RJ. Efficacy of bupropion for smoking cessation in non depressed smokers [abstract]. *J Addict Dis* 1994;**13**(4):249.

52. Hurt RD, Sachs DPL, Glover ED, Offord KP, Johnston JA, Dale LC, *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;**337**(17):1195–202.

53. Hertzberg MA, Moore SD, Feldman ME, Beckham JC. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. *J Clin Psychopharmacol* 2001;**21**(1):94–8.

54. Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998;**18**(4):297–308.

55. Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, *et al.* The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996;**335**(24):1792–8.

56. Fishbein L, O'Brien P, Hutson A, Theriaque D, Stacpoole PW, Flotte T. Pharmacokinetics and pharmacodynamic effects of nicotine nasal spray devices on cardiovascular and pulmonary function. *J Invest Med* 2000;**48**(6):435–40.

57. Lucini D, Bertocchi F, Malliani A, Pagani M. Autonomic effects of nicotine patch administration in habitual cigarette smokers: a double-blind, placebo-controlled study using spectral analysis of RR interval and systolic arterial pressure variabilities. *J Cardiovasc Pharmacol* 1998;**31**:714–20.

58. Neunteufl T, Heher S, Kostner K, Mitulovic G, Lehr S, Schmid RW, *et al.* Contribution of nicotine to acute endothelial dysfunction in long-term smokers. *J Am Coll Cardiol* 2001;**37** (2 Suppl A):275A–6A.

59. Working Group for the Study of Transdermal Nicotine in Patients with CAD. Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 1994;**154**(9):989–95.

60. Allen SS, Hatsukami D, Jensen J, Grillo M, Bliss R. Effects of treatment on cardiovascular risk among smokeless tobacco users. *Prev Med* 1995;**24**(4):357–62.

61. Sabha M, Tanus Santos JE, Toledo JCY, Cittadino M, Carlos Rocha J, Moreno H, Jr. Pharmacodynamics and drug action: transdermal nicotine mimics the smoking-induced endothelial dysfunction. *Clin Pharmacol Ther* 2000;**68**(2):167–74.

62. Keeley EC, Pirwitz MJ, Landau C, Lange RA, Hillis LD, Foerster EH, *et al.* Intranasal nicotine spray does not augment the adverse effects of cigarette smoking on myocardial oxygen demand or coronary arterial dimensions. *Am J Med* 1996;**101**(4):357–63.

63. Epifano L, Di Vincenzo A, Fanelli C, Porcellati F, Perriello G, De Feo P, *et al.* Effect of cigarette smoking and of a transdermal nicotine delivery system on glucoregulation in type 2 diabetes mellitus. *Eur J Clin Pharmacol* 1992;**43**(3):257–63.

64. Khoury Z, Comans P, Keren A, Lerer T, Gavish A, Tzivoni D. Effects of transdermal nicotine patches on ambulatory ECG monitoring findings: a double-blind study in healthy smokers. *Cardiovasc Drug Ther* 1996;**10**(2):179–84.

65. Krivokapich J, Schneider NG, Child JS, Jarvik ME. Cardiovascular effects of nicotine gum and cigarettes assessed by ECG and echocardiography. *Nida Res Monogr Ser* 1984;No. 53:42–55.

66. Tzivoni D, Khoury Z, Keren A, Brunel P, Lerer T. Cardiovascular safety of nicotine patches, as assessed by ambulatory electrocardiographic monitoring, in patients with coronary disease who try to quit smoking. *Eur Heart J* 1996; **17**(Abstr Suppl):310.

67. Hurt RD, Offord KP, Lauger GG, Marusic Z, Fagerstrom KO, Enright PL, *et al.* Cessation of long-term nicotine gum use – a prospective, randomized trial. *Addiction* 1995;**90**(3):407–13.

68. Jordan WP. Clinical evaluation of the contact sensitization potential of a transdermal nicotine system (Nicoderm). *J Family Pract* 1992;**34**(6):709–12.

69. Nordstrom BL, Kinnunen T, Utman CH, Garvey AJ. Long-term effects of nicotine gum on weight gain after smoking cessation. *Nicotine Tobacco Res* 1999;**1**(3):259–68.

70. West R, Hajek P, Foulds J, Nilsson F, May S, Meadows A. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacol Berl* 2000;**149**(3):198–202.

71. Oncken CA, Hardardottir H, Hatsukami DK, Lupo VR, Rodis JF, Smeltzer JS. Effects of transdermal nicotine or smoking on nicotine concentrations and maternal–fetal hemodynamics. *Obstet Gynecol* 1997;**90**(4 Pt 1):569–74.

72. Netscher DT, Wigoda P, Thornby J, Yip B, Rappaport NH. The hemodynamic and hematologic effects of cigarette smoking versus a nicotine patch. *Plast Reconstr Surg* 1995;**96**(3):681–8.

73. Zevin S, Jacob IP, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. *Clin Pharmacol Ther* 1998;**64**:87–95.

74. Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *Clin Pharmacol Ther* 1993;**53**(2):168.

75. Fredrickson PA, Hurt RD, Lee GM, Wingender L, Croghan IT, Lauger G, *et al.* High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels. *Psychopharmacology* 1995;**122**(3):215–22.

76. Gourlay SG, Forbes A, Marriner T, McNeil JJ. Predictors and timing of adverse experiences during transdermal nicotine therapy. *Drug Safety* 1999;**20**(6):545–55.

77. Hurt RD, Dale LC, Croghan GA, Croghan IT, Gomez Dahl LC, Offord KP. Nicotine nasal spray for smoking cessation: pattern of use, side effects, relief of withdrawal symptoms, and cotinine levels. *Mayo Clin Proc* 1998;**73**:118–25.

78. Bende M, Burian P, Danielsson GP, Kruse E, Millqvist E, Sawe U. Evaluation of side effects after nicotine nasal spray in patients with chronic rhinitis. *Rhinology* 1998;**36**(3):98–100.

79. Bjornson-Benson W, Nides M, Dolce J, Rand C, Lindgren P, O'Hara P, *et al.* Nicotine gum use in the first year of the Lung Health Study. *Addict Behav* 1993;**18**(4):491–502.

80. House RF, Smith TA, Croghan IT, Gauvin TR, Colligan RC, Offord KP, *et al.* A pilot-study of the safety of 22 mg nicotine patch therapy in adolescents [poster presentation]. *J Adolesc Health* 1995;**16**(2):142.

81. McNabb ME. Chewing nicotine gum for 3 months: what happens to plasma nicotine levels? *Can Med Assoc J* 1984;**131**(6):589–92.

82. Hatsukami D, Huber M, Callies A, Skoog K. Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology* 1993;**111**(4):449–56.

83. Wallstrom M, Sand L, Nilsson F, Hirsch JM. The long-term effect of nicotine on the oral mucosa. *Addiction* 1999;**94**(3):417–23.

84. Bircher AJ, Howald H, Rufli T. Adverse skin reactions to nicotine in a transdermal therapeutic system. *Contact Dermatitis* 1991;**25**(4):230–6.

85. Mills CM, Hill SA, Marks R. Transdermal nicotine suppresses cutaneous inflammation. *Arch Dermatol* 1997;**133**(7):823–5.

86. Sarabi M, Lind L. Short-term effects of smoking and nicotine chewing gum on endothelium-dependent vasodilation in young healthy habitual smokers. *J Cardiovasc Pharmacol* 2000;**35**(3):451–6.

87. Stein PK, Rottman JN, Kleiger RE. Effect of 21 mg transdermal nicotine patches and smoking cessation on heart rate variability. *Am J Cardiol* 1996;**77**:701–5.

88. Mahmarian JJ, Moye LA, Nasser GA, Nagueh SF, Bloom MF, Benowitz NL, *et al.* Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. *J Am Coll Cardiol* 1997;**30**(1):125–30.

89. Nitenberg A, Antony I. Effects of nicotine gum on coronary vasomotor responses during sympathetic stimulation in patients with coronary artery stenosis. *J Cardiovasc Pharmacol* 1999;**34**(5):694–9.

90. Moffatt RJ, Biggerstaff KD, Stamford BA. Effects of the transdermal nicotine patch on normalization of HDL-C and its subfractions. *Prev Med* 2000; **31**(2 Pt 1):148–52.

91. Schuh KJ, Schuh LM, Henningfield JE, Stitzer ML. Nicotine nasal spray and vapor inhaler: abuse liability assessment. *Psychopharmacology* 1997;**130**(4):352–61.

92. Ogburn Jr PL, Hurt RD, Croghan IT, Schroeder DR, Ramin KD, Offord KP, *et al.* Nicotine patch use in pregnant smokers: nicotine and cotinine levels and fetal effects. *Am J Obstet Gynecol* 1999;**181**(3):736–43.

93. Wright LN, Thorp JM, Kuller JA, Shrewsbury RP, Ananth C, Hartmann K. Transdermal nicotine replacement in pregnancy: maternal pharmacokinetics and fetal effects. *Am J Obstet Gynecol* 1997;**176**(5):1090–4.

94. Kimmel SE, Berlin JA, Miles C, Jaskowiak J, Carson JL, Strom BL. Risk of acute first myocardial infarction and use of nicotine patches in a general population. *J Am Coll Cardiol* 2001;**37**(5):1297–302.

95. Spyker DA, Alderfer RJ, Goetsch RA, Longmire AW, Kramer ED. Post-marketing adverse events associated with the nicotine patch and polacrilex resin in the United States. *Clin Pharmacol Ther* 1996;**59**(2):159.

96. Ottervanger JP, Wilson JHP, Stricker BHC. Drug-induced chest pain and myocardial infarction. Reports to a national centre and review of the literature. *Eur J Clin Pharmacol* 1997;**53**(2):105–10.

97. Medicines Control Agency. Zyban (bupropion hydrochloride) – safety update. In: (cited 2001 May). Medicines Control Agency, 2001. Available from URL: http://www.open.gov.uk/mca/index.htm

98. Novartis Consumer Health. Submission to the National Institute for Clinical Excellence for Bupropion HCl SR (Zyban) and nicotine replacement therapy to promote smoking cessation. Horsham: Novartis Consumer Health; July 2001.

99. GlaxoSmithKline. Submission to NICE for bupropion HCl SR (Zyban) and NiQuitin CQ (nicotine replacement therapy). Uxbridge: GlaxoSmithKline; July 2001.

100. Brandspigel K, Walsh MM. Nicotine induced exacerbation of duodenal ulcer. *Arch Intern Med* 1987;**147**(May):1001.

101. Dousset JC, Gutierres JB, Dousset N. Hypercholesterolaemia after administration of nicotine chewing gum. *Lancet* 1986;**2**(8520):1393–4.

102. Einarson TR, Einarson A. Hiccups following nicotine gum use. *Ann Pharmacother* 1997;**31**(10):1263–4.

103. Farm G. Contact allergy to nicotine from a nicotine patch. *Contact Dermatitis* 1993;**29**(4):214–15.

104. Foulds J, Toone B. A case of nicotine psychosis? *Addiction* 1995;**90**(3):435–7.

105. Frazier CA, Fiore MC, Hartman MJ. Side effects of nicotine patches. *JAMA* 1993;**270**(22):2735.

106. Goodman RP, Douglas CR. Rash from nicotine gum. *South Med J* 1987;**80**(4):539.

107. Jackson M. Cerebral arterial narrowing with nicotine patch. *Lancet* 1993;**342**(8865):236–7.

108. Lavaud F, Prevost A, Perdu D, Vallerand H, Deschamps F, Wong T. Nicotine transdermal therapeutic system patch and anaphylactoid reaction after a wasp sting. *South Med J* 1994;**87**(9):963.

109. Moreau T, Vukusic S, Vandenabeele S, Confavreux C. Nicotine et aggravation de la myasthenie [Nicotine and myasthenia gravis worsening]. *Rev Neurol* 1997;**153**(2):141–3.

110. Ottervanger JP, Festen JM, De Vries AG, Stricker BHC. Acute myocardial infarction while using the nicotine patch. *Chest* 1995;**107**(6):1765–6.

111. Pierce JR, Jr. Stroke following application of a nicotine patch. *Ann Pharmacother* 1994;**28**(3):402.

112. Sick L, Kopferschmitt J, Kintz P, Mangin P, Jaeger A. Le patch transdermique a la nicotine: quelques regles de prudence d'emploi, a propos d'une observation d'effets indesirables [The transdermal nicotine patch: certain precautions regarding its use, based upon a case of adverse reactions]. *J Med Strasbourg* 1993;**24**(5–6):183–4.

113. Stewart PM, Catterall JR. Chronic nicotine ingestion and atrial fibrillation. *Br Heart J* 1985;**54**(2):222–3.

114. Vincenzi C, Tosti A, Cirone M, Guarrera M, Cusano F. Allergic contact dermatitis from transdermal nicotine systems. *Contact Dermatitis* 1993;**29**(2):104–5.

115. Von Bahr B, Wahlberg JE. Reactivity to nicotine patches wrongly blamed on contact allergy. *Contact Dermatitis* 1997;**37**(1):44–5.

116. Warner Jr JG, Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. *Ann Intern Med* 1994;**120**(8):695.

117. Tzivoni D, Keren A, Meyler S, Khoury Z, Lerer T, Brunel P. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovasc Drugs Ther* 1998;**12**:239–44.

118. Wallstrom M, Sand L, Nilsson F, Hirsch JM. The long term effect of a nicotine sublingual tablet on the oral mucosa – a safety evaluation in a smoking cessation setting. *Eur Respir J* 1997;**10**(Suppl 25):440S.

119. Spyker DA, Alderfer RJ, Goetsch RA, Longmire AW, Kramer ED. Adverse events and prolonged use of nicotine gum and patch. *Nicotine Safety Toxicity* 1998:167–72.

120. Hardardottir H, Oncken C, Lupo VR, Daragjati C, Chang R, Smeltzer JS. Maternal and fetal cardiovascular effects of a nicotine-patch versus maternal smoking. *Am J Obstet Gynecol* 1996; **174**(1 Pt 2):367.

121. Tonnesen P, Paoletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, *et al.* Higher dosage nicotine patches increase one-year smoking cessation rates: Results from the European CEASE trial. *Eur Respir J* 1999;**13**:238–46.

122. Branconnier RJ, Cole JO, Oxenkrug GF, Ghazvinian S, Dessain EC, Spera KF, *et al.* Cardiovascular effects of imipramine and bupropion in aged depressed patients. *Psychopharmacol Bull* 1983;**19**(4):658–62.

123. Kiev A, Masco HL, Wenger TL, Johnston JA, Batey SR, Holloman LC. The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. *Ann Clin Psychiatry* 1994;**6**(2):107–15.

124. Roose SP, Glassman AH, Giardina EG, Johnson LL, Walsh BT, Bigger Jr JT. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol* 1987;**7**(4):247–51.

125. Batey S, Hughes AR, Ascher JA, Donahue RMJ. A comparison of the effects of bupropion SR and sertraline on sexual functioning in depressed outpatients. 11th European College of Neuropsychopharmacology Congress; 31 Oct–4 Nov 1998; Paris, France. S183.

126. Coleman CC, Cunningham LA, Foster VJ, Batey SR, Donahue RMJ, Houser TL, *et al.* Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann Clin Psychiatry* 1999;**11**(4):205–15.

127. Labbate LA, Brodrick PS, Nelson RP, Lydiard RB, Arana GW. Effects of bupropion sustained-release on sexual functioning and nocturnal erections in healthy men. *J Clin Psychopharmacol* 2001;**21**(1):99–103.

128. Segraves RT, Kavoussi R, Hughes AR, Batey SR, Johnston JA, Donahue R, *et al.* Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. *J Clin Psychopharmacol* 2000;**20**(2):122–8.

129. Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry* 1983;**44**(5 Pt 2):174–5.

130. Wenger TL, Stern WC. The cardiovascular profile of bupropion. *J Clin Psychiatry* 1983; **44**(5 Pt 2):176–82.

131. Roth MT, Westman EC. Safety of Zyban in patients with co-existing medical and/or psychiatric conditions. *J Invest Med* 1999;**47**(2):113A.

132. van Wyck Fleet J, Manberg PJ, Miller LL, Harto Truax N, Sato T, Fleck RJ, *et al.* Overview of clinically significant adverse reactions to bupropion. *J Clin Psychiatry* 1983;**44**(5 Pt 2):191–6.

133. Davidson J. Seizures and bupropion: a review. *J Clin Psychiatry* 1989;**50**(7):256–61.

134. Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry* 1998;**59**(7):366–73.

135. Johnston JA, Lineberry CG, Ascher JA, Davidson J, Khayrallah MA, Feighner JP, *et al.* A 102-center prospective study of seizure in association with bupropion. *J Clin Psychiatry* 1991;**52**(11):450–6.

136. Farid FF, Wenger TL, Tsai SY, Singh BN, Stern WC. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry* 1983;**44**(5 Pt 2):170–3.

137. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EGV. Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry* 1991;**148**(4):512–16.

138. Gardner EA. Effects of bupropion on weight in patients intolerant to previous antidepressants. *Curr Ther Res Clin Exp* 1984;**35**(2):188–99.

139. Gardner EA, Johnston JA. Bupropion: an antidepressant without sexual pathophysiological action. *J Clin Psychopharmacol* 1985;**5**(1):24–9.

140. Rowland DL, Myers L, Culver A, Davidson JM. Bupropion and sexual function: a placebo-controlled prospective study on diabetic men with erectile dysfunction. *J Clin Psychopharmacol* 1997;**17**(5):350–7.

141. Modell JG, Katholi CR, Modell JD, DePalma RL. Comparative sexual side effects of bupropion, fluoxetine, paroxetine, and sertraline. *Clinic Pharmacol Ther* 1997;**61**(4):476–87.

142. Therapeutic Goods Administration. Update on bupropion (Zyban SR) – 31 August 2001. URL: http://www.health.gov.au/tga/docs/html/zyban.htm

143. Hebert S. Bupropion (Zyban) sustained release tablets: reported adverse drug reactions. *Can Adv Drug React Newsl* 1999;**9**(2):1050–1.

144. Briggs GG, Samson JH, Ambrose PJ, Schroeder DH. Excretion of bupropion in breast milk. *Ann Pharmacother* 1993;**27**:431–3.

145. Amann B, Hummel B, Rall Autenrieth H, Walden J, Grunze H. Bupropion-induced isolated impairment of sensory trigeminal nerve function. *Int Clin Psychopharmacol* 2000;**15**(2):115–16.

146. Ames D, Wirshing WC, Szuba MP. Organic mental disorders associated with bupropion in three patients. *J Clin Psychiatry* 1992;**53**(2):53–5.

147. Balon R. Bupropion and nightmares. *Am J Psychiatry* 1996;**153**(4):579–80.

148. Bittman BJ, Young RC. Mania in an elderly man treated with bupropion. *Am J Psychiatry* 1991; **148**(4):541.

149. Dager SR, Heritch AJ. A case of bupropion-associated delirium. *J Clin Psychiatry* 1990;**51**(7):307–8.

150. David D, Esquenazi J. Rhabdomyolysis associated with bupropion treatment. *J Clin Psychopharmacol* 1999;**19**(2):185–6.

151. Fichtner CG, Braun BG, Zubieta JK, Demitrack MA. Bupropion-associated mania in a patient with HIV infection. *J Clin Psychopharmacol* 1992;**12**(5):366–7.

152. Gardos G. Reversible dyskinesia during bupropion therapy. *J Clin Psychiatry* 1997;**58**(5):218.

153. Golden RN, James SP, Sherer MA, Rudorfer MV, Sack DA, Potter WZ. Psychoses associated with bupropion treatment. *Am J Psychiatry* 1985;**142**(12):1459–62.

154. Goren JL, Levin GM. Mania with bupropion: a dose-related phenomenon? *Ann Pharmacother* 2000;**34**(5):619–21.

155. Halbreich U, Rojansky N, Bakhai Y, Wang K. Menstrual irregularities associated with bupropion treatment. *J Clin Psychiatry* 1991;**52**(1):15–16.

156. Howard WT, Warnock JK. Bupropion-induced psychosis. *Am J Psychiatry* 1999;**156**(12):2017–18.

157. Hu KQ, Tiyyagura L, Kanel G, Redeker AG. Acute hepatitis induced by bupropion. *Dig Dis Sci* 2000;**45**(9):1872–3.

158. Humma LM, Swims MP. Bupropion mimics a transient ischemic attack. *Ann Pharmacother* 1999;**33**:305–7.

159. Jackson CW, Head LA, Kellner CH. Catatonia associated with bupropion treatment. *J Clin Psychiatry* 1992;**53**(6):210.

160. Kanani AS, Kalicinsky C, Warrington RJ, Sussman G, Eisenstat J, Bowen TJ, *et al.* Serum sickness-like reaction with bupropion sustained release. *Can J Allergy Clin Immunol* 2000;**5**(1):27–29.

161. Labbate LA. Bupropion-SR-induced increased libido and spontaneous orgasm [letter]. *Can J Psychiatry* 1998;**43**(6):644–5.

162. Levenson JL. Priapism associated with bupropion treatment. *Am J Psychiatry* 1995;**152**(5):813.

163. Liberzon I, Dequardo JR, Silk KR. Bupropion and delirium. *Am J Psychiatry* 1990;**147**(12):1689–90.

164. Mainie I, McGurk C, McClintock G, Robinson J. Seizures after bupropion overdose. *Lancet* 2001;**357**:1624.

165. Malesker MA, Soori GS, Malone PM, Mahowald JA, Housel GJ. Eosinophilia associated with bupropion. *Ann Pharmacother* 1995;**29**(9):867–9.

166. Masand P, Stern TA. Bupropion and secondary mania: is there a relationship? *Ann Clin Psychiatry* 1993;**5**(4):271–4.

167. McCollom RA, Elbe DHT, Ritchie AH. Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000;**34**(4):471–3.

168. Paris PA, Saucier JR. ECG conduction delays associated with massive bupropion overdose. *J Toxicol Clin Toxicol* 1998;**36**(6):595–8.

169. Patten CA, Rummans TA, Croghan IT, Hurt RD, Hays JT. Development of depression during placebo-controlled trials of bupropion for smoking cessation: case reports. *J Clin Psychiatry* 1999;**60**(7):436–41.

170. Peloso PM, Baillie C. Serum sickness-like reaction with bupropion. *JAMA* 1999;**282**(19):1817.

171. Ramasubbu R. Bupropion treatment-related sexual side effects: a case report. *Can J Psychiat Rev Can Psychiatry* 2000;**45**(2):200.

172. Settle Jr EC. Tinnitus related to bupropion treatment. *J Clin Psychiatry* 1991;**52**(8):352.

173. Sheehan DV, Welch JB, Fishman SM. A case of bupropion-induced seizure. *J Nerv Ment Dis* 1986;**174**(8):496–8.

174. Szuba MP, Leuchter AF. Falling backward in two elderly patients taking bupropion. *J Clin Psychiatry* 1992;**53**(5):157–9.

175. Tripathi A, Greenberger PA. Bupropion hydrochloride induced serum sickness-like reaction. *Ann Allergy Asthma Immunol* 1999;**83**(2):165–6.

176. Van Putten T, Shaffer I. Delirium associated with bupropion. *J Clin Psychopharmacol* 1990;**10**(3):234.

177. Workman EA, Short DD. Bupropion-induced carbohydrate craving and weight gain. *Am J Psychiatry* 1992;**149**(10):1407–8.

178. Yolles JC, Armenta WA, Alao AO. Serum sickness induced by bupropion. *Ann Pharmacother* 1999;**33**(9):931–3.

179. Zubieta JK, Demitrack MA. Possible bupropion precipitation of mania and a mixed affective state. *J Clin Psychopharmacol* 1991;**11**(5):327–8.

180. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. *Am J Psychiatry* 1996;**153**(9):1132–7.

181. Peck AW, Stern WC, Watkinson C. Incidence of seizures during treatment with tricyclic anti-depressant drugs and bupropion. *J Clin Psychiatry* 1983;**44**(5 Pt 2):197–201.

182. Akehurst R, Piercy J. Cost-effectiveness of the use of Nicorette nasal spray to assist quitting smoking among heavy smokers. *Br J Med Econ* 1994; **7**:155–184.

183. Akehurst RL, Piercy J. Cost-effectiveness of the use of transdermal Nicorette patches relative to GP counselling and nicotine gum in the prevention of smoking related diseases. *Br J Med Econ* 1994;**7**:115–22.

184. Crealey GE, McElnay JC, Maguire TA, O'Neill C. Costs and effects associated with a community pharmacy-based smoking-cessation programme. *Pharmacoeconomics* 1998;**14**(3):323–33.

185. Orme ME, Hogue SL, Kennedy LM, Paine AC, Godfrey C. Development of the health and economic consequences of smoking interactive model. *Tobacco Control* 2001;**10**:55–61.

186. Stapleton JA, Lowin A, Russell MAH. Prescription of transdermal nicotine patches for smoking cessation in general practice: evaluation of cost-effectiveness. *Lancet* 1999;**354**(17):210–15.

187. Cromwell J, Bartosch WJ, Fiore MC, Hasselblad V, Baker T. Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. *JAMA* 1997;**278**(21):1759–66.

188. Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians' smoking cessation counselling. *JAMA* 1996;**275**(16):1247–51.

189. Oster G, Huse DM, Delea TE, Colditz GA. Cost effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking. *JAMA* 1986;**256**(10):1315–18.

190. Wasley MA, McNagny SE, Phillips VL, Ahluwalia JS. The cost-effectiveness of the nicotine transdermal patch for smoking cessation. *Prev Med* 1997;**26**:264–70.

191. Halpern MT, Khan ZM, Young TL, Battista C. Economic model of sustained-release bupropion hydrochloride in health plan and work site smoking-cessation programs. *Am J Health Syst Pharm* 2000;**57**(15):1421–9.

192. Nielsen K, Fiore MC. Cost–benefit analysis of sustained-release bupropion, nicotine patch, or both for smoking cessation. *Prev Med* 2000;**30**:209–16.

193. Buck DJ, Richmond RL, Mendelsohn CP. Cost-effectiveness analysis of a family physician delivered smoking cessation program. *Prev Med* 2000;**31**(6):641–8.

194. Croghan IT, Offord KP, Evans TW, Schmidt S, Gomez-Dahl LC, Schroeder DR, *et al.* Cost-effectiveness of treating nicotine dependence: the Mayo Clinic experience. *Mayo Clin Proc* 1997;**72**(10):917–24.

195. Cummings SR, Rubin SM, Oster G. The cost-effectiveness of counseling smokers to quit. *JAMA* 1989;**261**:75–9.

196. Curry SJ, Grothaus LC, McAfee T, Pabiniak C. Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. *N Engl J Med* 1998;**339**(10):673–9.

197. Gunning-Schepers L. The health benefits of prevention: a simulation approach. *Health Policy* 1989;**12**:1–255.

198. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;**309**(6959):901–11.

199. Centers for Disease Control and Prevention. Years of healthy life. *Stat Notes* 1995;**7**:1–14.

200. Doll R, Peto R. Mortality in relation to smoking: 20 years observation on male British doctors. *BMJ* 1976;**2**:1525–36.

201. Kenford SL, Fiore MC, Jorenby DE, Smith SS. Predicting smoking cessation: who will quit with and without the nicotine patch. *JAMA* 1994;**271**(8):589–94.

202. Stapleton JA, Russell MA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, *et al.* Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction* 1995;**90**(1):31–42.

203. Yudkin PL, Jones L, Lancaster T, Fowler GH. Which smokers are helped to give up smoking using transdermal nicotine patches? Results from a randomized, double-blind, placebo-controlled trial. *Br J Gen Pract* 1996;**46**(404):145–8.

204. Barendregt JJ, Bonneux L, van der Mass PS. The health care costs of smoking. *N Engl J Med* 1997;**337**:1052–7.

205. Hodgson TA. The health care costs of smoking [letter]. *N Engl J Med* 1998;**338**:470.

206. Fries JF. The health care costs of smoking [letter]. *N Engl J Med* 1998;**338**:471.

207. Heaney D. The health care costs of smoking [letter]. *N Engl J Med* 1998;**338**:471.

208. Leistikow BW, Miller TR. The health care costs of smoking [letter]. *N Engl J Med* 1998;**338**:471.

209. Sauter C. The health care costs of smoking [letter]. *N Engl J Med* 1998;**338**:471–2.

210. Cohen DR, Fowler GH. Economic implications of smoking cessation therapies. A review of economic appraisals. *Pharmacoeconomics* 1993;**4**(5):331–44.

211. Department of Health. Statistics on smoking cessation services in the Health Action Zones in England, April 1999 to March 2000. London: The Government Statistical Service; 2001.

212. Warner EA, Kosten TR, O'Connor PG. Pharmacotherapy for opioid and cocaine abuse. *Med Clin North Am* 1997;**81**(4):909–25.

213. Tengs TO, Adams ME, Pliskin JS, Safran DG, Siegel JE, Weinstein MC, *et al.* Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995;**15**(3):369–90.

214. Buck D, Morgan A. Smoking and quitting with aid of nicotine replacement therapies in the English adult population. *Eur J Publ Health* 2001;**11**:211–17.

215. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000;**321**:355–8.

216. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of RCTs. *J Clin Epidemiol* 1997;**50**:683–91.

217. Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, *et al.* Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *BMJ* 1993;**306**(6879):683–7.

218. Netten A. Unit costs of health and social care 2000. Canterbury, UK: Personal Social Services Research Unit, University of Kent, 2000.

219. Office of National Statistics. Population and vital statistics by area of usual residence in the United Kingdom. London: The Stationery Office; 1998. Series VS: No. 25, p. 1; No. 21.

220. 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**(3):205–14.

221. Addington J. Group treatment for smoking cessation among persons with schizophrenia. *Psychiatric Services* 1998;**49**(7):925–8.

222. Adnot S. Tobacco: an atherogenic, thrombogenic or spasmogenic factor? *Arch Mal Coeur Vaiss* 1998;**91**(V):53–8.

223. 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):1–8.

224. Ajac IK, Giroux LJ, Hill JA. Bupropion: study of treatment in depressed patients. *J Fla Med Assoc* 1983;**70**(5):356–60.

225. Alsagoff F, Lee HP. Nicotine-replacement products in smoking cessation: a review. *Singapore Med J* 1993;**34**(6):505–10.

226. Andersen S, Keller C, McGowan N. Smoking cessation: the state of the science. The utility of the transtheoretical model in guiding interventions in smoking cessation. *Online J Knowledge Synth Nursing* 1999;**6**.

227. Andolsek KM. Safety of nicotine patch for patients with cardiac disease. *Am Family Phys* 1997;**55**(4):1429–32.

228. Bupropion-related tinnitus. *Nurse Drug Alert* 1991;**15**(11):87.

229. Bupropion-associated menstrual irregularities. *Nurse Drug Alert* 1991;**15**(4):32.

230. Cardiac problems during the use of nicotine patch. *Geneesmiddelenbulletin* 1994;**28**(8):68.

231. Transdermal nicotine and stroke. *Nurse Drug Alert* 1994;**18**(8):57–8.

232. Nicotine patches safe. *Br J Cardiol* 1997;**4**(6):224.

233. Safety of the nicotine patch in cardiac patients. *Emerg Med* 1997;**29**(6):45–6.

234. Zyban-associated ADRs. *Nurse Drug Alert* 1999;**23**(8):58–9.

235. Aparici M, Fernandez Gonzalez AL, Alegria E. [Clonidine in the treatment of tobacco withdrawal. Comparison with nicotine chewing gum.] *Rev Clin Esp* 1994;**194**(6):453–6.

236. Areechon W, Punnotok J. Smoking cessation through the use of nicotine chewing gum: a double-blind trial in Thailand. *Clin Ther* 1988;**10**(2):183–6.

237. Ashenden R, Silagy C, Weller D. A systematic review of the effectiveness of promoting lifestyle change in general practice. *Family Practice* 1997;**14**(2):160–75.

238. Balfour D, Benowitz N, Fagerstrom K, Kunze M, Keil U. Diagnosis and treatment of nicotine dependence with emphasis on nicotine replacement therapy: a status report. *Eur Heart J* 2000;**21**(6):438–45.

239. Barrueco M, Torrecilla M, Maderuelo JA, Ruiz CJ, Mezquita MAH, Plaza MD. Valor predictivo de la abstinencia tabaquica a los 2 meses de tratamiento. [Two-month results are predictors of outcome in a smoking cessation program.] *Med Clin* 2001;**116**(7):246–50.

240. Batey S, Ascher JA, Donahue RMJ, Houser TL. Comparison of the safety and efficacy of bupropion sustained release and paroxetine in elderly depressed outpatients 11th European College of Neuropsychopharmacology Congress; 1998 31 Oct–4 Nov; Paris, France. Abstract P.1.192.

241. Batra A, Buchkremer G. [Smoking cessation with the nicotine patch.] *Z Arztl Fortbild Jena* 1995;**89**(5):505–9.

242. Becona E, Vazquez FL. Smoking cessation treatments in Spain. A thirty-year perspective: 1966–1996. *Substance Use Misuse* 2000;**35**(4):433–49.

243. Bello S. [Treatment of smoking.] *Rev Med Chile* 1991;**119**(6):701–8.

244. Benowitz NL. Toxicity of nicotine: implications with regard to nicotine replacement therapy. In: Pomerleau OF, Pomerleau CS, editors. Nicotine replacement: a critical evaluation. New York: Alan R Liss; 1988. p. 187–217.

245. Benowitz NL. Nicotine and coronary heart disease. *Trends Cardiovasc Med* 1991;**1**(8):315–21.

246. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol* 1997;**29**(7):1422–31.

247. Blondal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *Eur Respir J* 1997;**10**(7):1585–90.

248. Blondal T, Gudmundsson LJ, Tomasson K, Jonsdottir D, Hilmarsdottir H, Kristjansson F, *et al.* The effects of fluoxetine combined with nicotine inhalers in smoking cessation – a randomized trial. *Addiction* 1999;**94**(7):1007–15.

249. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 2000;**160**(20):3128–34.

250. Bolliger CT. Practical experiences in smoking reduction and cessation. *Addiction* 2000; **95**(Suppl 1):S19–24.

251. Bolliger CT, Zellweger JP, Danielsson T, Van Biljon X, Robidou A, Westin A, *et al.* Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *BMJ* 2000;**321**(7257):329–33.

252. Bonapace CR, Mays DA. The effect of mesalamine and nicotine in the treatment of inflammatory bowel disease. *Ann Pharmacother* 1997;**31**(7–8):907–13.

253. Borja Villegas J, Armet Sanpere G, Valles Planas JM. [Cardiovascular effects of antidepressants.] *Farm Clin* 1986;**3**(4):280–2.

254. Breckenbridge A. Zyban – modified dosage and safety precautions [letter]. 2001. CEM/CMO/2001/7.

255. Buchkremer G, Bents H, Minneker E, Opitz K. [Long-term effects of smoking cessation therapy combining behavior therapy and transdermal nicotine substitution.] *Nervenarzt* 1988;**59**(8):488–90.

256. Campbell IA, Prescott RJ, Tjeder Burton SM. Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study. *Respir Med* 1996;**90**(1):47–51.

257. Canive JM, Clark RD, Calais LA, Qualls C, Tuason VB. Bupropion treatment in veterans with posttraumatic stress disorder: an open study. *J Clin Psychopharmacol* 1998;**18**(5):379–83.

258. Carmody TP, Loew DE, Hall RG, Breckenridge JS, Breckenridge JN, Hall SM. Nicotine polacrilex: Clinic-based strategies with chronically ill smokers. *Journal of Psychoactive Drugs* 1988;**20**(3):269–74.

259. Cato AE, Cook L, Starbuck R, Heatherington D. Methodologic approach to adverse events applied to bupropion clinical trials. *J Clin Psychiatry* 1983;**44**(5 Pt 2):187–90.

260. Christen AG, McDonald JL Jr. Safety of nicotine-containing gum. In: Pomerleau OF, Pomerleau CS, editors. Nicotine replacement: a critical evaluation. Progress in clinical and biological research, Vol. 261. New York: Alan R. Liss; 1992. p. 219–35.

261. Clemens P, Baron JA, Coffey D, Reeves A. The short-term effect of nicotine chewing gum in patients with Parkinson's disease. *Psychopharmacology* 1995;**117**(2):253–6.

262. Clouse WD, Yamaguchi H, Phillips MR, Hurt RD, Fitzpatrick LA, Moyer TP, *et al.* Effects of transdermal nicotine treatment on structure and function of coronary artery bypass grafts. *J Appl Physiol* 2000;**89**(3):1213–23.

263. Conners CK, Levin ED, Sparrow E, Hinton SC, Erhardt D, Meck WH, *et al.* Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). *Psychopharmacol Bull* 1996;**32**(1):67–73.

264. Cooper TM, Clayton RR. Nicotine transdermal systems: efficacy, safety and effects on nicotine withdrawal symptoms. *Health Values* 1994;**18**(1):73–9.

265. Covey LS, Sullivan MA, Johnston JA, Glassman AH, Robinson MD, Adams DP. Advances in non-nicotine pharmacotherapy for smoking cessation. *Drugs* 2000;**59**(1):17–31.

266. Croft H, Settle E, Houser T, Batey SR, Donahue RMJ, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther* 1999;**21**(4):643–58.

267. Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. *Psychopharmacology Berl* 1995;**119**(2):193–204.

268. Dailey JW, Naritoku DK. Antidepressants and seizures: clinical anecdotes overshadow neuroscience. *Biochem Pharmacol* 1996;**52**(9):1323–9.

269. Dale LC, Hurt RD, Offord KP, Lawson GM, Croghan IT, Schroeder DR. High-dose nicotine patch therapy: percentage of replacement and smoking cessation. *JAMA* 1995;**274**(17):1353–8.

270. Danis PG, Seaton TL. Helping your patients to quit smoking. *Am Family Phys* 1997;**55**(4):1207–14.

271. Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, *et al.* Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Monaldi Mal Torace* 1992;**47**(1–6):17–29.

272. David S, Lancaster T, Stead LF. Narcotic antagonists for smoking cessation (Protocol for a Cochrane Review). In: The Cochrane Library 2001 Issue 2. Oxford: Update Software; 2001.

273. Davidson J, Miller R, Van Wyck Fleet J, Strickland R, Manberg P, Allen S, *et al.* A double-blind comparison of bupropion and amitriptyline in depressed inpatients. *J Clin Psychiatry* 1983;**44**(5 Pt 2):115–17.

274. Davidson M, Epstein M, Burt R, Schaefer C, Whitworth G, McDonald A. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. *Arch Family Med* 1998;**7**(6):569–74.

275. de Wit H, Zacny J. Abuse potential of nicotine replacement therapies. *CNS Drugs* 1995;**4**(6):456–68.

276. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001;**24**(4):277–322.

277. Dewan MJ, Anand VS. Evaluating the tolerability of the newer antidepressants. *J Nerv Ment Dis* 1999;**187**(2):96–101.

278. Dubois G. Les substituts nicotiniques: avec ou sans prescription medicale? [Nicotine substitutes: with or without drug prescription?] *Bull Acad Natl Med* 1999;**183**(6):1165–70.

279. Dufresne RL, Becker RE, Blitzer R, Waner RL, Lal H. Safety and efficacy of bupropion, a novel antidepressant. *Drug Dev Res* 1985;**6**(1):39–45.

280. Fabre LF, McLendon DM. Double-blind placebo-controlled study of bupropion hydrochloride (Wellbatrin®) in the treatment of depressed inpatients. *Curr Ther Res* 1978;**23**(3 Pt 2):393–402.

281. Fabre LF, Brodie HK, Garver D, Zung WW. A multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. *J Clin Psychiatry* 1983;**44**(5 Pt 2):88–94.

282. Fagerstrom KO. A comparison of psychological and pharmacological treatment in smoking cessation. *J Behav Med* 1982;**5**(3):343–51.

283. Fagerstrom KO, Hughes JR, Rasmussen T, Callas PW. Randomised trial investigating effect of a novel nicotine delivery device (Eclipse) and a nicotine oral inhaler on smoking behaviour, nicotine and carbon monoxide exposure, and motivation to quit. *Tobacco Control* 2000;**9**(3):327–33.

284. Fee WM, Stewart MJ. A controlled trial of nicotine chewing gum in a smoking withdrawal clinic. *Practitioner* 1982;**226**(1363):148–51.

285. Feighner JP, Meredith CH, Stern WC, Hendrickson G, Miller LL. A double-blind study of bupropion and placebo in depression. *Am J Psychiatry* 1984;**141**(4):525–9.

286. Feighner J, Hendrickson G, Miller L, Stern W. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharmacol* 1986;**6**(1):27–32.

287. Feighner JP, Gardner EA, Johnston JA, Batey SR, Khayrallah MA, Ascher JA, *et al.* Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J Clin Psychiatry* 1991;**52**(8):329–35.

288. Finkel SI. Efficacy and tolerability of antidepressant therapy in the old-old. *J Clin Psychiatry* 1996;**57**(Suppl 5):23–8.

289. Fiore MC, Hartman MJ. Side-effects of nicotine patches. *JAMA* 1993;**270**(22):2735.

290. Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Fox BJ, Goldstein MG. A clinical practice guideline for treating tobacco use and dependence: a US Public Health Service report. *JAMA* 2000;**283**(24):3244–54.

291. Fiore MC, Thompson SA, Lawrence DL, Welsch S, Andrews K, Ziarnik M, *et al.* Helping Wisconsin women quit smoking: a successful collaboration. *Wis Med J* 2000;**99**(2):68–72.

292. Fortmann SP, Killen JD, Telch MJ, Newman B. Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford Stop Smoking Project. *JAMA* 1988;**260**(11):1575–80.

293. Foulds J, Stapleton J, Hayward M, Russell MA, Feyerabend C, Fleming T, *et al.* Transdermal nicotine patches with low-intensity support to aid smoking cessation in outpatients in a general hospital. A placebo-controlled trial. *Arch Family Med* 1993;**2**(4):417–23.

294. Frenkel AR, Quitkin FM, Rabkin JG. Behavioral side effects associated with antidepressants and lithium. In: Kane JM, Lieberman JA, editors. Adverse effects of psychotropic drugs. New York: Guilford Press; 1992. p. 111–27.

295. Galvin K, Webb C, Hillier V. Assessing the impact of a nurse-led health education intervention for people with peripheral vascular disease who smoke: the use of physiological markers, nicotine dependence and withdrawal. *Int J Nurs Studies* 2001;**38**(1):91–105.

296. Gardner EA. Long-term preventive care in depression: the use of bupropion in patients intolerant of other antidepressants. *J Clin Psychiatry* 1983;**44**(5 Pt 2):157–62.

297. Gariti P, Alterman AI, Mulvaney FD, Epperson L. The relationship between psychopathology and smoking cessation treatment response. *Drug Alcohol Depend* 2000;**60**(3):267–73.

298. Gentry MV, Hammersley JJ, Hale CR, Nuwer PK, Meliska CJ. Nicotine patches improve mood and response speed in a lexical decision task. *Addict Behav* 2000;**25**(4):549–57.

299. George TR, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, *et al.* Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* 2000;**157**(11):1835–42.

300. Girdler SS, Jamner LD, Jarvik M, Soles JR, Shapiro D. Smoking status and nicotine administration differentially modify hemodynamic stress reactivity in men and women. *Psychosomatic Medicine* 1997;**59**(3):294–306.

301. Glavin GB, Dugani AM. Effects of dopamine agonists and antagonists on stress ulcer formation and gastric acid secretion. *Neuropharmacology* 1987;**46**(3):710.

302. Glover ED, Glover PN, Abrons HL, Franzon M. Smoking cessation among COPD and chronic bronchitis patients using the nicotine nasal spray. *Am J Health Behav* 1997;**21**(4):310–17.

303. Goldstein MG. Bupropion sustained release and smoking cessation. *J Clin Psychiatry* 1998; **59**(Suppl 4):66–72.

304. Gonzales D, Nides M, Ferry LH, Kustra R, Segall N, Herrero L. Retreating relapse: bupropion SR versus placebo in adult cigarette smokers previously treated with bupropion. In: US Society of Research on Nicotine and Tobacco; March 2001; Seattle, 2001.

305. Goodnick PJ. Acute and long-term bupropion therapy: response and side effects. *Ann Clin Psychiatry* 1991;**3**(4):311–13.

306. Gore AV, Chien YW. The nicotine transdermal system. *Clin Dermatol* 1998;**16**(5):599–615.

307. Gorman SE, Herrington LF, Geller RJ. An adverse event associated with nicotine detector patch. *J Toxicol Clin Toxicol* 1997;**35**(5):502.

308. Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ* 1995;**311**(7001):363–6.

309. Grandes G, Cortada JM, Arrazola A. An evidence-based programme for smoking cessation: effectiveness in routine general practice. *Br J Gen Pract* 2000;**50**(459):803–7.

310. Grossman F, Potter WZ, Brown EA, Maislin G. A double-blind study comparing idazoxan and bupropion in bipolar depressed patients. *J Affect Disord* 1999;**56**(2–3):237–43.

311. Hajek P, Jackson P, Belcher M. Long term use of nicotine chewing gum: occurrence, determinants, and effect on weight gain. *JAMA* 1988;**260**(11):1593–6.

312. Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Arch Intern Med* 1999;**159**:2033–8.

313. Halaris AE, Stern WC, Van Wyck Fleet J, Reno RM. Evaluation of the safety and efficacy of bupropion in depression. *J Clin Psychiatry* 1983; **44**(5 Pt 2):101–3.

314. Hamilton MJ, Smith PR, Peck AW. Effects of bupropion, nomifensine and dexamphetamine on performance, subjective feelings, autonomic variables and electroencephalogram in healthy volunteers. *Br J Clin Pharmacol* 1983;**15**:367–74.

315. Hamilton SP, Klimchak C, Nunes EV. Treatment of depressed methadone maintenance patients with nefazodone: a case series. *Am J Addict* 1998;**7**(4):309–12.

316. Harto Truax N, Van Wyck Fleet J, Stern WC. Double-blind comparison of bupropion vs. amitriptyline in depressed out-patients. *Psychopharmacol Bull* 1982;**18**(1):72–6.

317. Harto-Truax N, Stern WC, Miller LL, Sato TL, Cato AE. Effects of bupropion on body weight. *J Clin Psychiatry* 1983;**44**(5 Pt 2):183–6.

318. Hatsukami DK, Grillo M, Boyle R, Allen S, Jensen J, Bliss R, *et al.* Treatment of spit tobacco users with transdermal nicotine system and mint snuff. *J Consult Clin Psychol* 2000;**68**(2):241–9.

319. Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm* 1986;**5**:471–80.

320. Hays JT, Croghan IT, Schroeder DR, Offord KP, Hurt RD, Wolter TD, *et al.* Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled, and open label trials. *Am J Publ Health* 1999;**89**(11):1701–7.

321. Hays JT, Schroeder DR, Offord KP, Croghan IT, Patten CA, Hurt RD, *et al.* Response to nicotine dependence treatment in smokers with current and past alcohol problems. *Ann Behav Med* 1999;**21**(3):244–50.

322. Jorenby DE, Smith SS, Fiore MC, Hurt RD, Offord KP, Croghan IT, *et al.* Varying nicotine patch dose and type of smoking cessation counseling. *JAMA* 1995;**274**(17):1347–52.

323. Hays JT, Wolter TD, Eberman KM, Croghan IT, Offord KP, Hurt RD. Residential (inpatient) treatment compared with outpatient treatment for nicotine dependence. *Mayo Clin Proc* 2001;**76**(2):124–33.

324. Helge TD, Denelsky GY. Pharmacologic aids to smoking cessation. *Cleveland Clin J Med* 2000;**67**(11):818–24.

325. Henningfield JE, Michaelides T, Sussman S. Developing treatment for tobacco addicted youth – issues and challenges. *J Child Adolesc Subst Abuse* 2000;**9**(4):5–26.

326. Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerstrom KO. Nicotine gum, 2 and 4 mg, for nicotine dependence: a double-blind placebo-controlled trial within a behavior-modification support program. *Chest* 1995;**108**(2):447–51.

327. Hilleman DE, Mohiuddin SM, Delcore MG. Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. *J Clin Pharmacol* 1994;**34**(3):222–4.

328. Hjalmarson AI. Effect of nicotine chewing gum in smoking cessation. A randomized, placebo-controlled, double-blind study. *JAMA* 1984;**252**(20):2835–8.

329. Hjalmarson A, Franzon M, Westin A, Wiklund O. Effect of nicotine nasal spray on smoking cessation: a randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1994;**154**(22):2567–72.

330. Hjalmarson A, Nilsson F, Sjostrom L, Wiklund O. The nicotine inhaler in smoking cessation. *Arch Intern Med* 1997;**157**(15):1721–8.

331. Homsy W, Yan K, Houle JM, Besner JG, Gossard D, Pierce CH, *et al.* Plasma levels of nicotine and safety of smokers wearing transdermal delivery systems during multiple simultaneous intake of nicotine and during exercise. *J Clin Pharmacol* 1997;**37**(8):728–36.

332. Horne RL, Ferguson JM, Pope Jr HG, Hudson JI, Lineberry CG, Ascher J, *et al.* Treatment of bulimia with bupropion: a multicenter controlled trial. *J Clin Psychiatry* 1988;**49**(7):262–6.

333. Hughes S, Barnett S, Sosnouski P, Kirksey DF. A clinical trial of bupropion in the treatment of depressed outpatients. *Minn Med* 1984;**67**(9):501–5.

334. Hughes JR, Gust SW, Keenan RM, Fenwick JW, Healey ML. Nicotine vs placebo gum in general medical practice. *JAMA* 1989;**261**(9):1300–5.

335. Hughes JR. Transdermal nicotine – clarifications, side-effects, and funding. *JAMA* 1993; **269**(15):1939–41.

336. Hughes JR. Risk–benefit assessment of nicotine preparations in smoking cessation. *Drug Safety* 1993;**8**(1):49–56.

337. Hughes JR, Lesmes GR, Hatsukami DK, Richmond RL, Lichtenstein E, Jorenby DE, *et al.* Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tobacco Res* 1999;**1**(2):169–74.

338. Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine-replacement therapy with use of a transdermal nicotine patch – a randomized double-blind placebo-controlled trial. *Mayo Clin Proc* 1990;**65**(12):1529–37.

339. Hurt RD, Dale LC, Fredrickson PA, Caldwell CC, Lee GA, Offord KP, *et al.* Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: one-year outcome and percentage of nicotine replacement. *JAMA* 1994;**271**(8):595–600.

340. Hurt RD, Croghan GA, Beede SD, Wolter TD, Croghan IT, Patten CA. Nicotine patch therapy in 101 adolescent smokers: efficacy, withdrawal symptom relief, and carbon monoxide and plasma cotinine levels. *Arch Pediatr Adolesc Med* 2000;**154**(1):31–7.

341. Imperial Cancer Research Fund General Practice Research Group. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomized trial in general practice. *BMJ* 1993; **306**(6888):1304–8.

342. Jacobsen LK, Chappell P, Woolston JL. Bupropion and compulsive behavior. *J Am Acad Child Adolesc Psychiatry* 1994;**33**(1):143–4.

343. Jarvis MJ, Raw M, Russell MA, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. *Br Med J Clin Res Educ* 1982;**285**(6341):537–40.

344. Jensen EJ, Schmidt E, Pedersen B, Dahl R. Effect of nicotine, silver acetate, and ordinary chewing gum in combination with group counselling on smoking cessation. *Thorax* 1990;**45**(11):831–4.

345. Jimenez Ruiz CA, Florez S, Solano S, Ramos A, Ramos L, Fornies E. Nicotine gum (2 mg) plus counselling as treatment for smokers in a cessation clinic setting. *J Smok Relat Disord* 1994;**5**(3):171–5.

346. Jimenez Ruiz CA, Gonzalez de Vega JM, Escudero Bueno C, Solano S, Perez Trullen A, Garcia Hidalgo A, *et al.* [Results of a smoking cessation program among Spanish pulmonologists and thoracic surgeons.] *Arch Bronconeumol* 1996;**32**(3):138–41.

347. Jimenez Ruiz CA, Florez S, Ramos A, Ramos L, Solano S, Fornies E. Smoking cessation with a 16 h nicotine patch: results in a group of hospital workers. *Eur Respir J* 1997;**10**(3):573–5.

348. Jimenez Ruiz CA, Florez Martin S, Ramos Pineda A, Lorza JJ, Hernandez Mezquita MA, Solano Reina S, *et al.* [Nasal nicotine spray in smoking cessation. Results of a multicenter study.] *Arch Bronconeumol* 1999;**35**(11):535–8.

349. Jimenez Ruiz CA, Cisneros C, Perello Bosch O, Barruero Ferrero M, Hernandez Mezquita MA, Solano Reina S. Individualized treatment of smoking addiction. Results using 2 and 4 mg nicotine gum. *Arch Bronconeumol* 2000;**36**(3):129–32.

350. Jimenez Ruiz CA, Cisneros C, Perello Bosch O, Barruero Ferrero M, Hernandez Mezquita MA, Solano Reina S. Tratamiento individualizado del tabaquismo. Resultados con chicles de 2 y 4 mg de nicotina. [Individual treatment of smoking addiction. Results using 2 and 4 mg nicotine gum.] *Arch Bronconeumol* 2000;**36**(3):129–32.

351. Johnston JA, Lineberry CG, Frieden CS. Prevalence of psychosis, delusions, and hallucinations in clinical trials with bupropion [letter]. *Am J Psychiatry* 1986;**143**(9):1192–3.

352. Jorenby DE, Keehn, DS, Fiore MC. Comparative efficacy and tolerability of nicotine replacement therapies. *CNS Drugs* 1995;**3**(3):227–36.

353. Jorenby DE, Hatsukami DK, Smith SS, Fiore MC, Allen S, Jensen J, *et al.* Characterization of tobacco withdrawal symptoms: transdermal nicotine reduces hunger and weight gain. *Psychopharmacology* 1996;**128**(2):130–8.

354. Kalman D. Smoking cessation treatment for substance misusers in early recovery. *Substance Use Misuse* 1998;**33**(10):2021–47.

355. Kane JM, Cole K, Sarantakos S, Howard A, Borenstein M. Safety and efficacy of bupropion in elderly patients: preliminary observations. *J Clin Psychiatry* 1983;**44**(5 Pt 2):134–6.

356. Kavoussi RJ, Segraves RT, Hughes AR, Ascher JA, Johnston JA. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 1997;**58**(12):532–7.

357. Kellner CH, Pritchett JT, Jackson CW. Bupropion coadministration with electroconvulsive therapy: two case reports. *J Clin Psychopharmacol* 1994;**14**(3):215–16.

358. Killen JD, Fortmann SP, Davis L, Strausberg L, Varady A. Do heavy smokers benefit from higher dose nicotine patch therapy? *Exp Clin Psychopharmacol* 1999;**7**(3):226–33.

359. Killen JD, Fortmann SP, Schatzberg AF, Hayward C, Sussman L, Rothman M, *et al.* Nicotine patch and paroxetine for smoking cessation. *J Consult Clin Psychol* 2000;**68**(5):883–9.

360. Kinnell HG. Bupropion for smokers – drug is almost identical in structure to diethylpropion, a controlled drug. *BMJ* 2001;**322**(7283):431–2.

361. Kirksey DF, Harto Truax N. Private practice evaluation of the safety and efficacy of bupropion in depressed outpatients. *J Clin Psychiatry* 1983; **44**(5 Pt 2):143–7.

362. Kirksey DF, Stern WC. Multicenter private practice evaluation of the safety and efficacy of bupropion in depressed geriatric outpatients. *Curr Ther Res Clin Exp* 1984;**35**(2):200–10.

363. Kochak GM, Sun JX, Choi RL, Piraino AJ. Pharmacokinetic disposition of multiple-dose transdermal nicotine in healthy adult smokers. *Pharm Res* 1992;**9**(11):1451–5.

364. Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med* 1995;**24**(1):41–7.

365. Kupecz D, Prochazka A. A comparison of nicotine delivery systems in a multimodality smoking cessation program. *Nurse Pract* 1996;**21**(2):73–81.

366. Kwan AL, Meiners AP, van Grootheest AC, Lekkerkerker JF. [Risk of convulsions due to the use of bupropion as an aid for smoking cessation.] *Ned Tijdschr Geneeskd* 2001;**145**(6):277–8.

367. Labbate LA. Bupropion: antidepressant with prosexual effects? *Int Drug Ther Newsl* 1999;**34**:19–20.

368. Lagrue G, Verra F, Lebargy F, Jackson M. Nicotine patches and vascular risks. *Lancet* 1993;**342**(8870):564.

369. Lancaster T, Stead LF. Self-help interventions for smoking cessation (Cochrane Review). In: The Cochrane Library 2001 Issue 2. Oxford: Update Software; 2001.

370. Leigh R, Viner NM, Cox G, Balon JW, Wilson DM, O'Shaughnessy D, *et al.* Nicotine replacement combined with a novel compound (ProBAN) for smoking cessation: a pilot study. *Can Respir J* 2001;**8**(1):21–6.

371. Leischow SJ, Valente SN, Hill AL, Otte PS, Aickin M, Holden T, *et al.* Effects of nicotine dose and administration method on withdrawal symptoms and side effects during short-term smoking abstinence. *Exp Clin Psychopharmacol* 1997;**5**(1):54–64.

372. Levin ED, Westman EC, Stein RM, Carnahan E, Sanchez M, Herman S, *et al.* Nicotine skin patch treatment increases abstinence, decreases withdrawal symptoms, and attenuates rewarding effects of smoking. *J Clin Psychopharmacol* 1994;**14**(1):41–9.

373. Lewis SF, Piasecki TM, Fiore MC, Anderson JE, Baker TB. Transdermal nicotine replacement for hospitalized patients: a randomized clinical trial. *Prev Med* 1998;**27**(2):296–303.

374. Lineberry CG, Johnston JA, Raymond RN, Samara B, Feighner JP, Harto NE, *et al.* A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry* 1990;**51**(5):194–9.

375. Lockhart L, McMeeken K, Mark J, Cross S, Tait G, Isles C. Secondary prevention after myocardial infarction: reducing the risk of further cardiovascular events. *Coronary Health Care* 2000;**4**(2):82–91.

376. López-Arrieta JM, Rodríguez JL, Sanz F. Efficacy and safety of nicotine on Alzheimer's disease patients (Cochrane Review). In: The Cochrane Library 2001 Issue 2. Oxford: Update Software; 2001.

377. Lumley J, Oliver S, Waters E. Interventions for promoting smoking cessation during pregnancy (Cochrane Review). In: The Cochrane Library Issue 4. Oxford: Update Software; 2000.

378. Margolin A, Kosten T, Petrakis I, Kelly Avants S. An open pilot study of bupropion and psychotherapy for the treatment of cocaine abuse in methadone-maintained patients. *Nida Res Monogr Ser* 1990;**105**:367–8.

379. Margolin A, Kosten TR, Avants SK, Wilkins J, Ling W, Beckson M, *et al.* A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depend* 1995;**40**(2):125–31.

380. Martin PD, Robinson GM. The safety, tolerability and efficacy of transdermal nicotine (Nicotinell TTS) in initially hospitalised patients. *NZ Med J* 1995;**108**(992):6–8.

381. Murray RP, Bailey WC, Daniels K, Bjornson WM, Kurnow K, Connett JE, *et al.* Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest* 1996;**109**(2):438–45.

382. Martin K, Froelicher ES, Miller NH. Women's Initiative for Nonsmoking (WINS) II: the intervention. *Heart Lung* 2000;**29**(6):438–45.

383. Masco HL, Kiev A, Holloman LC, Batey SR, Johnston JA, Lineberry CG. Safety and efficacy of bupropion and nortriptyline in outpatients with depression. *Curr Ther Res Clin Exp* 1994;**55**(7):851–63.

384. Matsushima D, Prevo ME, Gorsline J. Absorption and adverse effects following topical and oral administration of three transdermal nicotine products to dogs. *J Pharm Sci* 1995;**84**(3):365–9.

385. McGovern PG, Lando HA. An assessment of nicotine gum as an adjunct to freedom from smoking cessation clinics. *Addict Behav* 1992;**17**(2):137–47.

386. McNabb ME, Ebert RV, McCusker K. Plasma nicotine levels produced by chewing nicotine gum. *JAMA* 1982;**248**(7):865–8.

387. Mendels J, Amin MM, Chouinard G, Cooper AJ, Miles JE, Remick RA, *et al.* A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry* 1983;**44**(5 Pt 2):118–20.

388. Merideth CH, Feighner JP. The use of bupropion in hospitalized depressed patients. *J Clin Psychiatry* 1983;**44**(5 Pt 2):85–7.

389. Mielke MM, Jorenby DE, Fiore MC. Achieving smoking cessation in nicotine-dependent individuals – practical guidelines. *CNS Drugs* 1997;**8**(1):12–20.

390. Mintz J, Phipps CC, Arruda MJ, Glynn SM, Schneider NG, Jarvik ME. Combined use of alcohol and nicotine gum. *Addict Behav* 1991;**16**(1–2):1–10.

391. Mittmann N, Herrmann N, Shulman KI, Silver IL, Busto UE, Borden EK, *et al.* The effectiveness of antidepressants in elderly depressed outpatients: a prospective case series study. *J Clin Psychiatry* 1999;**60**(10):690–7.

392. Montalto NJ, Garrett SD. Utilization of nicotine nasal spray in smoking cessation. *J Am Osteopath Assoc* 1998;**98**(3):160–4.

393. Montoya ID, Preston KL, Cone EJ, Rothman R, Gorelick DA. Safety and efficacy of bupropion combined with bromocriptine for treatment of cocaine dependence. *Am J Addict* 1996;**5**(1):69–75.

394. Moxham J. Nicotine addiction: should be recognised as the central problem of smoking. *BMJ* 2000;**320**(7232):391–2.

395. Murray RP, Anthonisen NR. Interventions for smoking cessation: the outcomes are determined by the questions asked. *Eur Respir J* 1999;**13**(2):231–2.

396. Murray RP, Gerald LB, Lindgren PG, Connett JE, Rand CS, Anthonisen NR. Characteristics of participants who stop smoking and sustain abstinence for 1 and 5 years in the Lung Health Study. *Prev Med* 2000;**30**(5):392–400.

397. Namerow LB, Tilton P, Horrigan JP. Seizure associated with bupropion and guanfacine [multiple letters]. *J Am Acad Child Adolesc Psychiatry* 1999;**38**(1):2–3.

398. Norman TR, Maguire KP, Burrows GD. New antidepressants: clinical studies. *Adv Human Psychopharmacol* 1984;**3**:3–27.

399. Odishaw J, Chen C. Effects of steady-state bupropion on the pharmacokinetics of lamotrigine in healthy subjects. *Pharmacotherapy* 2000;**20**(12):1448–53.

400. O'Hara P, Grill J, Rigdon MA, Connett JE, Lauger GA, Johnston JJ. Design and results of the initial intervention program for the Lung Health Study. *Prev Med* 1993;**22**(3):304–15.

401. Okuyemi KS, Ahluwalia JS, Harris KJ. Pharmacotherapy of smoking cessation. *Arch Family Med* 2000;**9**(3):270–81.

402. Oliver A. What populations are at risk when taking bupropion? *Mont Pharm* 1993;**17**:18–19.

403. Orleans CT, Resch N, Noll E, Keintz MK, Rimer BK, Brown TV, *et al.* Use of transdermal nicotine in a state-level prescription plan for the elderly. *JAMA* 1994;**271**(8):601–7.

404. Othmer E, Othmer SC, Stern WC, Van Wyck Fleet J. Long-term efficacy and safety of bupropion. *J Clin Psychiatry* 1983;**44**(5 Pt 2):153–6.

405. Patel DR, Greydanus DE. Office interventions for adolescent smokers. *Adolesc Med State Art Rev* 2000;**11**(3):577–88.

406. Patten CA. A critical evaluation of nicotine replacement therapy for teenage smokers. *J Child Adolesc Subst Abuse* 2000;**9**(4):51–75.

407. Patten CA, Martin JE, Calfas KJ, Brown SA, Schroeder DR. Effect of three smoking cessation treatments on nicotine withdrawal in 141 abstinent alcoholic smokers. *Addict Behav* 2000;**25**(2):301–6.

408. Pearlstein TB, Stone AB, Lund SA, Scheft H, Zlotnick C, Brown WA. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol* 1997;**17**(4):261–6.

409. Perkins KA, Grobe JE, D'Amico D, Fonte C, Wilson AS, Stiller RL. Low-dose nicotine nasal spray use and effects during initial smoking cessation. *Exp Clin Psychopharmacol* 1996;**4**(2):157–65.

410. Perkins KA. Smoking cessation in women: special considerations. *CNS Drugs* 2001;**15**(5):391–411.

411. Piasecki TM, Fiore MC, Baker TB. Profiles in discouragement: two studies of variability in the time course of smoking withdrawal symptoms. *J Abnorm Psychol* 1998;**107**(2):238–51.

412. Pickworth WB, Herning RI, Henningfield JE. Electroencephalographic effects of nicotine chewing gum in humans. *Pharmacol Biochem Behav* 1986;**25**(4):879–82.

413. Pitts WM, Fann WE, Halaris AE, Dressler DM, Sajadi C, Snyder S, *et al.* Bupropion in depression: a tri-center placebo-controlled study. *J Clin Psychiatry* 1983;**44**(5 Pt 2):95–100.

414. Preskorn SH, Othmer SC. Evaluation of bupropion hydrochloride: the first of a new class of atypical antidepressants. *Pharmacotherapy* 1984;**4**(1):20–34.

415. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry* 1995;**56**(Suppl 6):12–21.

416. Ramasubbu R. Switching to moclobemide to reverse fluoxetine-induced sexual dysfunction in patients with depression. *J Psychiatry Neurosci* 1999;**24**(1):45–50.

417. Raw M, Jarvis MJ, Feyerabend C, Russell MA. Comparison of nicotine chewing-gum and psychological treatments for dependent smokers. *BMJ* 1980;**281**(6238):481–2.

418. Reimherr FW, Cunningham LA, Batey SR, Johnston JA, Ascher JA. A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. *Clin Ther* 1998;**20**(3):505–16.

419. Remick RA, Campos PE, Misri S, Miles JE, Van Wyck Fleet J. A comparison of the safety and efficacy of bupropion HCl and amitriptyline HCl in depressed outpatients. *Prog Neuropsychopharmacol Biol Psychiatry* 1982;**6**:523–7.

420. Rennard SI, Daughton DM. Smoking cessation. *Chest* 2000;**117**(5 Suppl 2):360s–64s.

421. Rennard S, Hatsukami D, Malcolm R, Patel MK, Jamerson BD, Dozier G. A multicenter study examining the effects of Zyban (bupropion HCl SR) vs. placebo as an aid to smoking reduction leading to cessation among smokers unwilling and unable to quit smoking: methods. Seattle, WA: US Society of Research on Nicotine and Tobacco; 2001.

422. Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. *Med J Aust* 1994;**161**(2):130–5.

423. Richmond RL. A comparison of measures used to assess effectiveness of the transdermal nicotine patch at 1 year. *Addict Behav* 1997;**22**(6):753–7.

424. Richmond RL. Physicians can make a difference with smokers: evidence-based clinical approaches. *Int J Tuberculosis Lung Dis* 1999;**3**(2):100–12.

425. Riggs PD, Leon SL, Mikulich SK, Pottle LC. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. *J Am Acad Child Adolesc Psychiatry* 1998;**37**(12):1271–8.

426. Ritvo PG, Irvine MJ, Lindsay EA, Kraetschmer N, Blair N, Shnek ZM. A critical review of research related to family physician-assisted smoking cessation interventions. *Cancer Prev Control* 1997;**1**(4):289–303.

427. Rose JE, Herskovic JE, Trilling Y, Jarvik ME. Transdermal nicotine reduces cigarette craving and nicotine preference. *Clin Pharmacol Ther* 1985;**38**(4):450–6.

428. Rose JE, Levin ED, Behm FM, Adivi C, Schur C. Transdermal nicotine facilitates smoking cessation. *Clin Pharmacol Ther* 1990;**47**(3):323–30.

429. Rose JE, Levin ED. Concurrent agonist–antagonist administration for the analysis and treatment of drug dependence. *Pharmacol Biochem Behav* 1991;**41**:219–26.

430. Rose JE, Behm FM, Westman EC. Nicotine–mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Exp Clin Psychopharmacol* 1998;**6**(3):331–43.

431. Rose JE, Behm FM, Westman EC. Brand-switching and gender effects in mecamylamone/nicotine smoking cessation treatment. *Nicotine Tobacco Res* 1999;**1**:286–7.

432. Rosenstein DL, Nelson JC, Jacobs SC. Seizures associated with antidepressants – a review. *J Clin Psychiatry* 1993;**54**(8):289–99.

433. Rudorfer MV, Manji HK, Potter WZ, Dequardo JR, Liberzon I, Silk KR. Bupropion, ECT, and dopaminergic overdrive. *Am J Psychiatry* 1991;**148**(8):1101–2.

434. Rudorfer MV, Manji HK, Potter WZ. Comparative tolerability profiles of the newer versus older antidepressants. *Drug Safety* 1994;**10**(1):18–46.

435. Russell MAH, Stapleton JA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, *et al.* Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ* 1993;**306**(6888):1308–12.

436. Sachs DPL, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med* 1993;**153**(16):1881–90.

437. Sachs GS, Lafer B, Stoll AL, Banov M, Thibault AB, Tohen M, *et al.* A double-blind trial of bupropion versus desipramine for bipolar depression. *J Clin Psychiatry* 1994;**55**(9):391–3.

438. Saenghirunvattana S. Trial of transdermal nicotine patch in smoking cessation. *J Med Assoc Thailand* 1995;**78**(9):466–8.

439. Salin-Pascual RJ, de la Fuente JR, Galicia-Polo L, Drucker-Colin R. Effects of transdermal nicotine on mood and sleep in nonsmoking major depressed patients. *Psychopharmacology* 1995;**121**(4):476–9.

440. Salvador Llivina T, Marin Tuya D, Gonzalez Quintana J, Iniesta Torres C, Castellvi Barrera E, Muriana Saez C, *et al.* [Smoking cessation: effectiveness of nicotine containing chewing gum. A double-blind trial.] *Med Clin Barc* 1988;**90**(16):646–50.

441. Sampablo Lauro I, Lores L, Coll F, Rebasa P. Combining nicotine patches and bupropion in smoking cessation therapy. *Arch Bronconeumol* 2000;**36**(7):377–80.

442. Sarko J. Antidepressants, old and new: a review of their adverse effects and toxicity in overdose. *Emerg Med Clin N Am* 2000;**18**(4):637–54.

443. Sawe U. Are there any contraindications for nicotine replacement therapy? *Eur Respir J* 1997;**10**(Suppl 25):124S.

444. Schneider NG, Olmstead R, Mody FV, Doan K, Franzon M, Jarvik ME, *et al.* Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. *Addiction* 1995;**90**(12):1671–82.

445. Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. *Addiction* 1996;**91**(9):1293–306.

446. Selby P, Brosky G, Baker R, Lertzman M, Dakin P, Roberts J. Zyban® is effective in the retreatment of relapsed adult smokers. Seattle, WA: US Society of Research on Nicotine and Tobacco; 2001.

447. Semenchuk MR, Davis B. Efficacy of sustained-release bupropion in neuropathic pain: an open-label study. *Clin J Pain* 2000;**16**(1):6–11.

448. Settle ECJ. Bupropion sustained release: side effect profile. *J Clin Psychiatry* 1998;**59**(Suppl 4):32–6.

449. Settle EC, Stahl SM, Batey SR, Johnston JA, Ascher JA. Safety profile of sustained-release bupropion in depression: results of three clinical trials. *Clin Ther* 1999;**21**(3):454–63.

450. Shaw JP, Ferry DG, Pethica D, Brenner D, Tucker IG. Usage patterns of transdermal nicotine when purchased as a non-prescription medicine from pharmacies. *Tobacco Control* 1998;**7**(2):161–7.

451. Shiffman S, Elash CA, Paton SM, Gwaltney CJ, Paty JA, Clark DB, *et al.* Comparative efficacy of 24-hour and 16-hour transdermal nicotine patches for relief of morning craving. *Addiction* 2000;**95**(8):1185–95.

452. Shiffman S, Paty JA, Rohay JM, Di Marino ME, Gitchell J. The efficacy of computer-tailored smoking cessation material as a supplement to nicotine polacrilex gum therapy. *Arch Intern Med* 2000;**160**(11):1675–81.

453. Shopsin B, Soper R, Tyrer S, van Wyck Fleet J, Stern W. Bupropion (Wellbutrin®)-imipramine study: a single-blind comparison in depressed outpatients. *Curr Ther Res Clin Exp* 1983; **33**(3):339–61.

454. Shuster J. Getting the word out: adverse consequences of nicotine replacement therapy. *Hosp Pharm* 1997;**32**(3):337–58.

455. Shuster J. Adverse drug reaction. Nicotine polacrilex gum. *Nursing* 1997;**27**(10):76.

456. Silagy C, Stead LF. Physician advice for smoking cessation (Cochrane Review). The Cochrane Library 2001 Issue 2. Oxford: Update Software; 2001.

457. Silver AA, Shytle RD, Philipp MK, Sanberg PR. Case study: long-term potentiation of neuroleptics with transdermal nicotine in Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 1996;**35**(12):1631–6.

458. Sinusas K, Coroso JG. Smokeless tobacco cessation: report of a preliminary trial using nicotine chewing gum. *J Family Pract* 1993;**37**(3):264–7.

459. Sivyer G, Gardiner J, Hibbins G, Saunders R. Smoking cessation study involving a transdermal nicotine patch. Outcomes achieved in a workplace setting and in general practice. *Drug Invest* 1994;**7**(5):244–53.

460. Smith EW, Smith KA, Maibach HI, Andersson PO, Cleary G, Wilson D. The local side-effects of transdermally absorbed nicotine. *Skin Pharmacol* 1992;**5**(2):69–76.

461. Smith TM, Winters FD. Smoking cessation: a clinical study of the transdermal nicotine patch. *J Am Osteopath Assoc* 1995;**95**(11):655–62.

462. Smith TA, House RF Jr, Croghan IT, Gauvin TR, Colligan RC, Offord KP, *et al.* Nicotine patch therapy in adolescent smokers. *Pediatrics* 1996;**98**(4):659–67.

463. Sonderskov J, Olsen J, Sabroe S, Meillier L, Overvad K. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. *Am J Epidemiol* 1997;**145**(4):309–18.

464. Spencer T, Biederman J, Steingard R, Wilens T. Bupropion exacerbates tics in children with attention-deficit hyperactivity disorder and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 1993;**32**(1):211–14.

465. Spiller HA, Ramoska EA, Krenzelok EP, Sheen SR, Borys DJ, Villalobos D. Bupropion overdose: a 3 year multi-center retrospective analysis. *Am J Emerg Med* 1994;**12**(1):43–5.

466. Stead LF, Lancaster T. Telephone counselling for smoking cessation (Cochrane Review). The Cochrane Library 2001 Issue 2. Oxford: Update Software; 2001.

467. Stern WC, Harto Truax N, Rogers J, Miller L. Clinical profile of the novel antidepressant bupropion. *Adv Biochem Psychopharmacol* 1982;**32**:21–34.

468. Stoll AL, Mayer PV, Kolbrener M, Goldstein E, Suplit B, Lucier J, *et al.* Antidepressant-associated mania: a controlled comparison with spontaneous mania. *Am J Psychiatry* 1994;**151**(11):1642–5.

469. Strecher VJ. Computer-tailored smoking cessation materials: a review and discussion. *Patient Educ Counsel* 1999;**36**(2):107–17.

470. Sudan BJL. Comment: niacin, nicotine, and flushing. *Ann Pharmacother* 1994;**28**(9):1113.

471. Sudan BJL. Nicotine skin patch treatment and adverse reactions – skin irritation, skin sensitization, and nicotine as a hapten. *J Clin Psychopharmacol* 1995;**15**(2):145–6.

472. Sutherland G, Stapleton JA, Russell MA, Jarvis MJ, Hajek P, Belcher M, *et al.* Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992;**340**(8815):324–9.

473. Tennstedt D, Lachapelle JM. Cutaneous adverse effects of transdermal therapeutic systems. *Rev Franc Allerg Immunol Clin* 1998;**38**(4):379–84.

474. Thomas GAO, Rhodes J, Mani V, Williams GT, Newcombe RG, Russell MAH, *et al.* Transdermal nicotine as maintenance therapy for ulcerative colitis. *N Engl J Med* 1995;**332**(15):988–92.

475. Thorton WP. Safety and effectiveness of nicotine chewing gum for smoking cessation. *Government Reports Announcements & Index* 1986;**3**:53.

476. Thorsteinsson HS, Gillin JC, Patten CA, Golshan S, Sutton LD, Drummond S, *et al.* The effects of transdermal nicotine therapy for smoking cessation on depressive symptoms in patients with major depression. *Neuropsychopharmacology* 2001;**24**(4):350–8.

477. Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnersen AB, Forchammer H, *et al.* Two and four mg nicotine chewing gum and group counselling in smoking cessation: an open, randomized, controlled trial with a 22 month follow-up. *Addict Behav* 1988;**13**(1):17–27.

478. Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med* 1991;**325**(5):311–15.

479. Tonnesen P, Norregaard J, Simonsen K, Sawe U. [A double-blind trial of nicotine patches in smoking cessation.] *Ugeskr-Laeger* 1992;**154**(5):251–4.

480. Tonnesen P, Norregaard J, Mikkelsen K, Jorgensen S, Nilsson F. A double-blind trial of a nicotine inhaler for smoking cessation. *JAMA* 1993;**269**(10):1268–71.

481. Tonnesen P, Norregaard J, Sawe U, Simonsen K. Recycling with nicotine patches in smoking cessation. *Addiction* 1993;**88**(4):533–9.

482. Tonnesen P, Mikkelsen K, Norregaard J, Jorgensen S. Recycling of hard-core smokers with nicotine nasal spray. *Eur Respir J* 1996;**9**(8):1619–23.

483. Tonnesen P. Smoking cessation: nicotine replacement, gums and patches. *Monaldi Arch Chest Dis* 1999;**54**(6):489–94.

484. Toral J, Ortega F, Cejudo P, Gualberto MR, Sanchez H, Montemayor T. Efficacy after six months of a smoking cessation program using combined nicotine replacement therapy (patches plus chewing gum). *Arch Bronconeumol* 1998;**34**:281–4.

485. Transdermal Nicotine Study Group. Transdermal nicotine for smoking cessation – 6-month results from 2 multicenter controlled clinical trials. *JAMA* 1991;**266**(22):3133–8.

486. Trappler B, Miyashiro AM. Bupropion–amantadine-associated neurotoxicity. *J Clin Psychiatry* 2000;**61**(1):61–2.

487. Tsoh JY, McClure JB, Skaar KL, Wetter DW, Cinciripini PM, Prokhorov AV, *et al.* Smoking cessation: 2. Components of effective intervention. *Behav Med* 1997;**23**(1):15–27.

488. Tsoh JY, Humfleet GL, Munoz RF, Reus VI, Hartz DT, Hall SM. Development of major depression after treatment for smoking cessation. *Am J Psychiatry* 2000;**157**(3):368–74.

489. Tucker WE. Preclinical toxicology of bupropion: an overview. *J Clin Psych* 1983;**44**(5 Pt 2):60–2.

490. van den Berkmortel FWPJ, Bootsma GP, Heijdra YF, van Spiegel PI, Wollersheim H. Smoking cessation: which aids are worthwhile? *Neth J Med* 2000;**57**(5):198–205.

491. Van Der Klauw MM, Stricker BHC. Local and systemic skin reactions to nicotine patches. *Ned Tijdschr Geneeskd* 1994;**138**(32):1628–31.

492. Van Ree JW. Nicotine containing chewing gum as an aid to give up smoking; experiences in a general practice. *Ned Tijdschr Geneeskd* 1984;**128**(41):1931–3.

493. Vida S, Looper K. Precision and comparability of adverse event rates of newer antidepressants. *J Clin Psychopharmacol* 1999;**19**(5):416–26.

494. Vieregge P, Sieberer M, Jacobs H, Hagenah J. Efficacy and tolerability of transdermal nicotine patches in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled study. *Neurology* 2000;**54**(Suppl 3):A278.

495. Vleggaar FP, van Buuren HR, Henegouwen G, Hop WCJ, van Erpecum KJ. No beneficial effects of transdermal nicotine in patients with primary sclerosing cholangitis: results of a randomized placebo-controlled cross-over study. *J Hepatol* 2000;**32**:131.

496. Wallstrom M, Nilsson F, Hirsch JM. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. *Addiction* 2000;**95**(8):1161–71.

497. Walsh RA. Effects of maternal smoking on adverse pregnancy outcomes: examination of the criteria of causation. *Human Biol* 1994;**66**(6):1059–92.

498. Wadland WC, Soffelmayr B, Ives K. Enhancing smoking cessation of low-income smokers in managed care. *J Family Pract* 2001;**50**(2):138–44.

499. Weihs KL, Settle Jr EC, Batey SR, Houser TL, Donahue RMJ, Ascher JA. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psychiatry* 2000;**61**(3):196–202.

500. Weiner E, Ball MP, Summerfelt A, Gold J, Buchanan RW. Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. *Am J Psychiatry* 2001;**158**(4):635–7.

501. Weisler RH, Johnston JA, Lineberry CG, Samara B, Branconnier RJ, Billow AA. Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 1994;**14**(3):170–9.

502. West R, Willis N. Double-blind, placebo-controlled trial of dextrose tablets and nicotine patch in smoking cessation. *Psychopharmacology* 1998;**136**:201–4.

503. West R, Hajek P, Nilsson F, Foulds J, May S, Meadows A. Individual differences in preferences for and responses to four nicotine replacement products. *Psychopharmacology* 2001;**153**(2):225–30.

504. Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation: a randomized trial with telephone counseling. *Arch Intern Med* 1993;**153**(16):1917–23.

505. Westman EC, Behm FM, Rose JE. Airway sensory replacement combined with nicotine replacement for smoking cessation: a randomized, placebo-controlled trial using a citric acid inhaler. *Chest* 1995;**107**(5):1358–64.

506. Wewers ME. Current concepts in smoking cessation and preventive strategies. *Sem Respir Crit Care Med* 1999;**20**(4):321–30.

507. White AD, Andrews EB. The Pregnancy Registry program at Glaxo Wellcome Company. *J Allergy Clin Immunol* 1999;**103**(2 Pt 2):S362–3.

508. Whiteman PD, Peck AW, Fowle ASE, Smith P. Bupropion fails to affect plasma prolactin and growth hormone in normal subjects. *Br J Clin Pharmacol* 1982;**13**:743–5.

509. Wilson AL, Langley LK, Monley J, Bauer T, Rottunda S, McFalls E, *et al.* Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. *Pharmacol Biochem Behav* 1995;**51**(2–3):509–14.

510. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Arch Intern Med* 2000;**160**(7):939–44.

511. Wolf R, Tuzun B, Tuzun Y. Adverse skin reactions to the nicotine transdermal system. *Clin Dermatol* 1998;**16**(5):617–23.

512. Wong PW, Kadakia SC, McBiles M. Acute effect of nicotine patch on gastric emptying of liquid and solid contents in healthy subjects. *Dig Dis Sci* 1999;**44**(11):2165–71.

513. Wongwiwatthananukit S, Jack HM, Popovich NG. Smoking cessation: Part 2 – Pharmacologic approaches. *J Am Pharm Assoc* 1998;**38**(3):339–53.

514. Zajecka J. Strategies for the treatment of antidepressant-related sexual dysfunction. *J Clin Psychiatry* 2001;**62**(Suppl 3):35–43.

515. Zhu SH, Tedeschi G, Anderson CM, Rosbrook B, Byrd M, Johnson CE, *et al.* Telephone counseling as adjuvant treatment for nicotine replacement therapy in a 'real-world' setting. *Prev Med* 2000;**31**(4):357–63.

516. Zobrist RH, Marriott JG, Nordbrock E, Hague B, Sachs DPL. Nicotine administration with a new oral transmucosal delivery system: a dose-response study. *Pharm Res* 1996;**13**(9 Suppl):S-325.

517. Zobrist H, Marriott JG, Gilbert R, Epstein MS, Pappas J. Preliminary 8-week safety and efficacy of oral transmucosal nicotine (OT-nicotine) compared to patch and gum for smoking cessation. *Addiction* 1998;**93**(6):923.

518. Zung WW, Brodie HK, Fabre L, McLendon D, Garver D. Comparative efficacy and safety of bupropion and placebo in the treatment of depression. *Psychopharmacol Berl* 1983;**79**(4):343–7.

519. Doherty K, Militello FS, Kinnunen T, Garvey AJ. Nicotine gum dose and weight gain after smoking cessation. *J Consult Clin Psychol* 1996;**64**:799–807.

520. Halpern MT, Khan ZM, Young TL, Battista C. Economic model of sustained-release bupropion hydrochloride in health plan and work site smoking-cessation programs. *Am J Health Syst Pharm* 2000;**57**(19):1421–9.

521. Krumholz H, Cohen BJ, Tsevat J, Pasternak RC, Weinstein MC. Cost-effectiveness of a smoking cessation program after myocardial infarction. *JACC* 1993;**22**:1697–702.

522. McGhan WF, Smith MD. Pharmacoeconomic analysis of smoking cessation interventions. *Am J Health Syst Pharm* 1996;**53**:45–52.

Appendix 1

Search strategies

Literature searches

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 clinical effectiveness, cost-effectiveness and safety of bupropion SR (Zyban) and NRT for smoking cessation. A total of 25 electronic databases were searched, and searches of the World Wide Web were also undertaken.

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

Structure of the searches

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

A search strategy was then devised to identify any newly published **RCTs** in order to update the references retrieved in 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 2000 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:

1. "Bupropion"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. smok* or tobacco or nicotin*
5. #3 and #4
6. nicotine replacement therap*
7. nrt
8. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
9. #6 or #7 or #8
10. #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.

Databases

The databases searched for each aspect of the review are presented in *Table 26*.

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 website (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/)

TABLE 26 *The databases searched for each aspect of the review*

Database (host)	Systematic reviews	RCTs	Adverse effects studies	Cost-effectiveness studies
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/)		✔		
DARE (http://nhscrd.york.ac.uk/)	✔		✔	
DHData (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 Pharmacopoeia (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 Sciences Citation Index (Web of Science)		✔	✔	
TOXLINE (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE)			✔	

were searched for information on pharmacology, dosage and clinical indications.

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 following key terms were used:

- zyban
- amfebutamone
- bupropion
- wellbutrin
- nrt
- nicotine

Search results were sifted by hand.

Search strategies

Systematic reviews

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

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

MEDLINE, CINAHL, EMBASE and PsycLIT 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 DARE. Thus MEDLINE, CINAHL, EMBASE and PsycLIT were searched from 2000 onwards in order to identify any existing systematic reviews that had not yet been included on the DARE database of systematic reviews.

Cochrane Database of Systematic Reviews (CD-ROM; Cochrane Library, 2001, Issue 2)

The search was done on 3 May 2001.

1. bupropion:me
2. zyban
3. amfebutamone
4. bupropion
5. buproprion
6. wellbutrin
7. #1 or #2 or #3 or #4 or #5 or #6
8. smok* or tobacco or nicotin*
9. #7 and #8
10. nicotine next replacement next therap*
11. nrt
12. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
13. #9 or #10 or #11 or #12

DARE (administrative database) and HTA Database (public version)

Both searches were done on 3 May 2001.

1. bupropion/subject heading
2. zyban/all fields
3. amfebutamone/all fields
4. bupropion/all fields
5. buproprion/all fields
6. wellbutrin/all fields
7. #1 or #2 or #3 or #4 or #5 or #6
8. (smok* or tobacco or nicotin*)/all fields
9. #7 and #8
10. nicotine replacement therap*/all fields
11. nrt/all fields
12. nicotin*(5w)(patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
13. #9 or #10 or #11 or #12

MEDLINE (SilverPlatter and PubMed)

The search was done on 3 May 2001 for the period 2000 to May 2001.

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

CINAHL (SilverPlatter)

The search was done on 3 May 2001 for the period 2000 to February 2001.

1. "Bupropion"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. smok* or tobacco or nicotin*
5. #3 and #4
6. nicotine replacement therap*
7. nrt
8. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
9. #6 or #7 or #8
10. #5 or #9
11. review* or overview*
12. metaanalys*
13. meta analys*
14. metanalys*
15. "Review-Literature"
16. "Systematic-Review"/ all topical subheadings / all age subheadings
17. #11 or #12 or #13 or #14 or #15 or #16
18. #10 and #17
19. #18 in ti,ab,de
20. #19 and (PY >= "2000")

EMBASE (SilverPlatter)

The search was on 3 May 2001 for the period 2000 to February 2001.

1. "amfebutamone"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin

3. #1 or #2
4. smok* or tobacco or nicotin*
5. #3 and #4
6. nicotine replacement therap*
7. nrt
8. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
9. #6 or #7 or #8
10. #5 or #9
11. review* or overview*
12. metaanalys*
13. meta analys*
14. metanalys*
15. "review"/ all subheadings
16. systematic review* or overview*
17. #11 or #12 or #13 or #14 or #15 or #16
18. #10 and #17
19. #18 and (PY >= "2000")

PsycLIT (WebSpirs)

The search was done on 3 May 2001 for the period 2000 to May 2001.

1. zyban
2. amfebutamone
3. bupropion
4. buproprion
5. wellbutrin
6. #1 or #2 or #3 or #4 or #5
7. smok* or tobacco or nicotin*
8. #6 and #7
9. nicotine next replacement next therap*
10. nrt
11. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
12. #8 or #9 or #10 or #11
13. review* or overview*
14. metaanalys*
15. meta analys*
16. metanalys*
17. #13 or #14 or #15 or #16
18. #12 and #17
19. #18 and (PY >= "2000")

RCTs

Literature searches were carried out in order to identify RCTs that 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) and National Research Register (CD-ROM; 2001, Issue 1)

The search of the Cochrane Controlled Trials Register was done on 2 May 2001. That of the National Research Register was done on 3 May 2001 and the results were sifted by hand for RCTs.

1. bupropion:me
2. zyban
3. amfebutamone
4. bupropion
5. buproprion
6. wellbutrin
7. #1 or #2 or #3 or #4 or #5 or #6
8. smok* or tobacco or nicotin*
9. #7 and #8
10. nicotine next replacement next therap*
11. nrt
12. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
13. #9 or #10 or #11 or #12

MEDLINE (SilverPlatter and PubMed)

The search was done on 3 May 2001 for the period 2000 to May 2001.

1. "Bupropion"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. smok* or tobacco or nicotin*
5. #3 and #4
6. nicotine replacement therap*
7. nrt
8. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
9. #6 or #7 or #8
10. #5 or #9
11. pt = "randomized-controlled-trial"
12. pt = "controlled-clinical-trial"
13. "Randomized-Controlled-Trials"/ all subheadings
14. "Random-Allocation"
15. "double-blind-method"/ all subheadings
16. "single-blind-method"/ all subheadings
17. pt = "clinical-trial"
18. explode "Clinical-Trials"/ all subheadings
19. (clin* near trial*) in ti,ab
20. (singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
21. "Placebos"/ all subheadings
22. placebo* in ti,ab
23. random* in ti,ab
24. "Research-Design"/ all subheadings
25. "Random-Allocation"
26. (control* near (trial* or stud*)) in ti,ab, mesh
27. crossover in ti,ab,mesh
28. explode "Evaluation-Studies"/ all subheadings
29. tg=comparative-study
30. #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
31. editorial in pt

32. comment in pt
33. letter in pt
34. tg = "animal"
35. tg = "human"
36. #34 not (#34 and #35)
37. #30 not (#31 or #32 or #33 or #36)
38. #10 and #37
39. #38 and (py>= "2000")

EMBASE (SilverPlatter)

The search was done on 2 May 2001 for the period 2000 to February 2001.

1. "amfebutamone"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. smok* or tobacco or nicotin*
4. nicotine replacement therap*
5. nrt
6. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
7. (#1 or #2) and #3
8. #4 or #5 or #6
9. #7 or #8
10. "randomized-controlled-trial"/ all subheadings
11. "randomization"/ all subheadings
12. "double-blind-procedure"/ all subheadings
13. "single-blind-procedure"/ all subheadings
14. "crossover-procedure"/ all subheadings
15. explode "clinical-trial"/ all subheadings
16. clin* near trial*
17. (singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
18. "placebo"/ all subheadings
19. placebo* in ti,ab
20. random* in ti,ab
21. control* near (trial* or stud*)
22. crossover
23. rct*
24. #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
25. #9 and #24
26. #25 and (py>= "2000")
27. explode "animal"/ all subheadings
28. explode "human"/ all subheadings
29. #27 not (#27 and #28)
30. #26 not #29

PsycLIT (WebSpirs); and HELMIS, DHData, King's Fund Database and CANCERLIT (all SilverPlatter)

All searches were done on 3 May 2001 for the following periods: PsycLIT, 2000 to May 2001; HELMIS, 1998 to 2000; DHData and the King's Fund Database, 2000 to February 2001; and CANCERLIT, 2000 to March 2001.

1. zyban
2. amfebutamone
3. bupropion
4. buproprion
5. wellbutrin
6. #1 or #2 or #3 or #4 or #5
7. smok* or tobacco or nicotin*
8. #6 and #7
9. nicotine next replacement next therap*
10. nrt
11. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
12. #8 or #9 or #10 or #11
13. clin* near trial*
14. (singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
15. placebo* in ti,ab
16. random* in ti,ab
17. control* near (trial* or stud*)
18. crossover
19. rct*
20. #13 or #14 or #15 or #16 or #17 or #18 or #19
21. #12 and #20
22. #21 and (py>= "2000")

CINAHL (SilverPlatter)

The search was done on 2 May 2001 for the period 2000 to February 2001.

1. "Bupropion"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. smok* or tobacco or nicotin*
5. #3 and #4
6. nicotine replacement therap*
7. nrt
8. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
9. #6 or #7 or #8
10. #5 or #9
11. explode "Clinical-Trials"/ all topical subheadings / all age subheadings
12. randomi?ed near2 (trial* or stud*)
13. placebo*
14. (doubl* or singl* or trebl* or tripl*) near2 (blind* or mask*)
15. rct*
16. exact{clinical-trial} in dt
17. clin* near trial*
18. "Placebos"/ all topical subheadings / all age subheadings
19. control* near (trial* or stud*)
20. crossover
21. #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
22. #10 and #21

23. #10 in ti,ab,de
24. #21 in ti,ab,de
25. #23 and #24
26. #25 and (py >= "2000")

Science Citation Index, Social Science Citation Index and Index to Scientific and Technical Proceedings (all Web of Science); BIOSIS (Edina)
All searches were done on 3 May 2001 for the period 2000 to May 2001.

1. (((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
This database can be found at http://www.controlledtrials.com. The search was done on 3 May 2001 for the period 2000 to May 2001.

1. bupropion or zyban or amfebutamone or buproprion or wellbutrin
2. smok* or tobacco or nicotin*
3. #1 and #2
4. nicotine replacement therapy or nrt
5. nicotin* and (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
6. #3 or #4 or #5

Adverse-effects studies

Literature searches for the adverse effects and safety of bupropion and NRT were designed to retrieve only trials wherever possible. However, the search of 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 or NRT. This search was only conducted on databases of systematic reviews (DARE, Cochrane Database of Systematic Reviews) and on databases on which search strategies had previously been limited by study type (MEDLINE, EMBASE). The administrative database of DARE was searched, rather than the public (Internet-based) version, in order to retrieve details of systematic reviews that 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 cessation. 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)
The search was done on 9 April 2001 for the period 1966 to December 2000.

RCT search
1. "Bupropion"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. side effect* or safety
5. adverse near3 (effect* or reaction* or event*)
6. #4 or #5
7. #3 and #6
8. "Bupropion"/ adverse-effects
9. #7 or #8
10. nicotine replacement therapy or nrt
11. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
12. #10 or #11
13. #12 and #6
14. #9 or #13
15. explode "Epidemiologic-Studies"/ all subheadings
16. explode "Clinical-Trials"/ all subheadings
17. #15 or #16
18. #14 and #17

Systematic review search
1. "Bupropion"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. side effect* or safety
5. adverse near3 (effect* or reaction* or event*)
6. #4 or #5
7. #3 and #6
8. "Bupropion"/ adverse-effects
9. #7 or #8
10. nicotine replacement therapy or nrt
11. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
12. #10 or #11
13. #12 and #6
14. #9 or #13
15. review or overview
16. data synthesis
17. published studies in ab
18. data extraction in ab

19. "Meta-Analysis"
20. meta analysis in ti
21. comment in pt
22. letter in pt
23. editorial in pt
24. animal in tg
25. human in tg
26. #24 not (#24 and #25)
27. #14 not (#21 or #22 or #23 or #26)
28. #15 or #16 or #17 or #18 or #19 or #20
29. #27 and #28

EMBASE (SilverPlatter)

The search was done on 9 April 2001 for the period 1980 to February 2001.

RCT search

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

Systematic review search

1. "amfebutamone"/ all subheadings
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. (side effect* in ti,ab) or safety
5. adverse near3 (effect* or reaction* or event*)
6. #4 or #5
7. #3 and #6
8. "amfebutamone"/ adverse-drug-reaction
9. #7 or #8
10. nicotine replacement therapy or nrt
11. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
12. #10 or #11
13. #12 and #6
14. #9 or #13
15. metaanalys*
16. meta analys*
17. metanalys*
18. systematic review*
19. #15 or #16 or #17 or #18
20. #14 and #19

CINAHL (SilverPlatter)

The search was done on 9 April 2001 for the period 1982 to December 2000.

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

HELMIS, DHData, King's Fund Database and AMED (all SilverPlatter); PsycLIT (WebSpirs)

Searches were done on 9 April 2001 for: HELMIS, for the period 1984 to 1998; DHData, for the period 1983 to February 2001; the King's Fund Database, for the period 1979 to February 2001; and AMED, for the period 1985 to December 2001. PsycLIT was searched on 17 April 2001 for the period 1969 to April 2001.

1. zyban or amfebutamone or bupropion or buproprion or wellbutrin
2. adverse near3 (effect* or reaction* or event*)
3. side effect* or safety
4. #2 or #3
5. #1 and #4
6. nicotine replacement therapy or nrt
7. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
8. #6 or #7
9. #8 and #4
10. #5 or #9

Science Citation Index, Social Sciences Citation Index and Index to Scientific and Technical Proceedings (all Web of Science); and BIOSIS (Edina)

All searches were done on 9 April 2001, for the periods: Science Citation Index and Social Sciences Citation Index, 1981 to April 2001;

Index to Scientific and Technical Proceedings, 1990 to April 2001; and BIOSIS, 1993 to April 2001.

1. (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)
The search was done on 9 April 2001.

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

Toxline (Dialog)
The search was done on 9 April 2001 for the period 1965 to April 2001. MEDLINE duplicates were removed in line 11 of the search.

1. s bupropion or zyban or amfebutamone or buproprion or wellbutrin
2. s side(w)effect? or safety
3. s adverse(5w)(effect? or reaction? or event?)
4. s s2 or s3
5. s s1 and s4
6. s nicotine(w)replacement(w)therapy or nrt
7. s nicotine(5w)(patch? or gum or inhaler? or spray? or tablet? or transdermal or lozenge?)
8. s s6 or s7
9. s s4 and s8
10. s s5 or s9
11. s s10/nonmed

Martindale Pharmacopoeia (Datastar)
The most recent available edition (32nd edition, April 1999) was searched on 18 April 2001.

1. bupropion or zyban or amfebutamone or buproprion or wellbutrin
2. side adj effect$ or safety
3. (adverse near (effect$ or reaction$ or event$)).rf.
4. 2 or 3
5. 1 and 4
6. nicotine adj replacement adj therapy or nrt
7. nicotine near (patch$ or gum or inhaler$ or spray$ or tablet$ or transdermal or lozenge$)
8. 6 or 7
9. 4 and 8
10. 5 or 9

DARE (administrative database)
The search was done on 9 April 2001.

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

Cochrane Database of Systematic Reviews (CD-ROM; Cochrane Library, 2001 Issue 2)
The search was done on 9 April 2001.

1. bupropion:me
2. zyban or amfebutamone or bupropion or buproprion or wellbutrin
3. #1 or #2
4. side effect* or safety
5. adverse near (effect* or reaction* or event*)
6. #4 or #5
7. #3 and #6
8. nicotine replacement therapy or nrt
9. nicotin* near (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
10. #8 or #9
11. #10 and #6
12. #7 or #11

Cost-effectiveness studies

Searches were carried out on a range of specialist economic evaluation databases in order to identify any records that 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 DHData were searched to identify any additional specifically UK-based cost-effectiveness data. The administrative database of NHS Economic Evaluation Database was searched rather than the public (Internet-based) version, in order to retrieve details of economic evaluations that did not meet the quality inclusion criteria for the database.

NHS Economic Evaluation Database (administrative database)
The search was done on 18 May 2001.

1. zyban or bupropion or wellbutrin or amfebutamone or buproprion
2. nicotine(w)replacement(w)therap$ or nrt
3. nicotine(3w)(patch$ or gum or inhaler$ or spray$ or tablet$ or transdermal or lozenge$)
4. 1 or 2 or 3

HTA Database (public database)
The search was done on 18 May 2001.

1. (zyban or bupropion or wellbutrin or amfebutamone or buproprion)/all fields
2. (nicotine(w)replacement(w)therap$ or nrt)/all fields
3. (nicotine(3w)(patch$ or gum or inhaler$ or spray$ or tablet$ or transdermal or lozenge$))/all fields
4. 1 or 2 or 3
5. cost$ or econom$ or pharmacoeconom$ or price$ or pricing
6. 4 or 5

Health Economic Evaluation Database (CD-ROM; Office of Health Economics) and EconBase (web interface)
EconBase can be found at http://www.elsevier.com/homepage/sae/econbase/menu.sht. Both searches were done on 18 May 2001.

1. 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, HELMIS, DHData and King's Fund Database (all SilverPlatter)
The searches were done on 18 May 2001, for the periods: EconLIT, 1969 to March 2001; HELMIS, 1984 to 1998; DHData, 1983 to March 2001; and King's Fund Database,1979 to March 2001.

1. zyban or bupropion or wellbutrin
2. nicotine replacement therap*
3. nicotine near3 (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)
4. buproprion or amfebutamone
5. #1 or #2 or #3
6. #1 or #2 or #3 or #4
7. cost* or econom* or pharmacoeconom* or price* or pricing
8. #6 and #7

Appendix 2
Excluded studies

TABLE 27 *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
Abelin *et al.*, 1989[220]	NRT	Efficacy study
Addington, 1998[221]	Neither	Non-systematic review
Adnot, 1998[222]	Neither	Very general review (and French)
Ahluwalia *et al.*, 1998[223]	NRT	Efficacy
Ajac *et al.*, 1983[224]	Bupropion	Efficacy study
Alsagoff and Lee, 1993[225]	NRT	General review
Andersen *et al.*, 1999[226]	Neither	Not about NRT of bupropion
Andolsk, 1997[227]	NRT	Not original article
Anon., 1991[228]	Bupropion	Not original article, see Settle, 1991[172]
Anon., 1991[229]	Bupropion	Not original article, see Halbreich *et al.*, 1991[155]
Anon., 1994[230]	NRT	Not original article
Anon., 1994[231]	NRT	Not original paper, see Pierce, 1994[111]
Anon., 1997[232]	NRT	Not original article
Anon., 1997[233]	NRT	Very brief comment type article; no references
Anon., 1999[234]	Bupropion	Not original article
Aparici *et al.*, 1994[235]	NRT	In Spanish; old RCT of efficacy
Areechon and Punnotok, 1988[236]	NRT	Efficacy study
Ashenden *et al.*, 1997[237]	Neither	Not specifically related to NRT or bupropion
Balfour *et al.*, 2000[238]	NRT	Non-systematic review
Barrueco *et al.*, 2001[239]	NRT	Not a direct comparative study of NRT; not in English
Batey *et al.*, 1998[240]	Bupropion	Antidepressant efficacy study
Batra and Buchkremer, 1995[241]	NRT	In German
Becona and Vazquez, 2000[242]	Neither	Focused on extent and number of publications
Bello, 1991[243]	NRT	Review; in Spanish
Benowitz, 1988[244]	NRT	Non-systematic review
Benowitz, 1991[245]	NRT	Brief review
Benowitz and Gourlay, 1997[246]	NRT	Non-systematic review of cardiovascular risk with NRT
Blondal *et al.*, 1997[247]	NRT	Efficacy study
Blondal *et al.*, 1999[248]	Neither	Efficacy study of fluoxetine in smoking cessation
Bohadana *et al.*, 2000[249]	NRT	Included in the latest update of the Cochrane Review of NRT (3rd edition, 2001)[26]
Bolliger, 2000[250]	Neither	Non-systematic review
Bolliger *et al.*, 2000[251]	NRT	Included in the latest update of the Cochrane Review of NRT (3rd edition, 2001)[26]
Bonapace and Mays, 1997[252]	NRT	Review of efficacy in inflammatory bowel disease
Borja Villegas *et al.*, 1986[253]	Bupropion	Review; in Spanish
Breckenridge, 2001[254]	Bupropion	Not original data
Brown *et al.*, 2000[2]	NRT	Non-systematic review
Buchkremer *et al.*, 1988[255]	NRT	Old efficacy study
Campbell, 1996[256]	NRT	Efficacy study

continued

***TABLE* 27 contd** *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
Canive *et al.*, 1998[257]	Bupropion	Efficacy study
Carmody *et al.*, 1988[258]	NRT	Efficacy study
Cato *et al.*, 1983[259]	Bupropion	Methodology paper; bupropion used merely as an example
Christen and McDonald, 1992[260]	NRT	Non-systematic review
Cinciripini and McClure, 1998[7]	Neither	Non-systematic review
Clemens *et al.*, 1995[261]	NRT	Efficacy study of NRT on symptoms of Parkinson's disease
Clouse *et al.*, 2000[262]	NRT	Study in dogs
Conners *et al.*, 1996[263]	NRT	Efficacy in attention deficit hyperactivity disorder
Cooper and Clayton, 1994[264]	NRT	Non-systematic review
Covey *et al.*, 2000[265]	Bupropion	Non-systematic review
Croft *et al.*, 1999[266]	Bupropion	Primarily an efficacy study
Crowley *et al.*, 1995[267]	NRT	Efficacy study
Dailey and Naritoku, 1996[268]	Bupropion	Non-systematic review; references checked
Dale *et al.*, 1995[269]	NRT	Efficacy study
Danis and Seaton, 1997[270]	Neither	Non-systematic review
Daughton *et al.*, 1992[271]	NRT	Efficacy study; in Italian
David *et al.*, 2001[272]	Neither	Protocol of Cochrane Review
Davidson *et al.*, 1983[273]	Bupropion	Antidepressant efficacy study
Davidson *et al.*, 1998[274]	NRT	Old efficacy study
de Wit and Zancy, 1995[275]	NRT	Non-systematic review of abuse potential
Dempsey and Benowitz, 2001[276]	NRT	Review of nicotine in pregnancy
Dewan and Anand, 1999[277]	Bupropion	Used *Physician's Desk Reference* data to rank antidepressants; not based on real data
Dubois, 1999[278]	NRT	Non-systematic review
Dufresne *et al.*, 1985[279]	Bupropion	Primarily an efficacy study
Fabre *et al.*, 1978[280]	Bupropion	Efficacy study
Fabre *et al.*, 1983[281]	Bupropion	Antidepressant efficacy study
Fagerstrom, 1982[282]	NRT	Efficacy study
Fagerstrom *et al.*, 2000[283]	NRT	Included in the latest update of the Cochrane Review of NRT (3rd edition, 2001)[26]
Fee and Stewart, 1982[284]	NRT	Efficacy study
Feighner *et al.*, 1984[285]	Bupropion	Efficacy study
Feighner *et al.*, 1986[286]	Bupropion	Efficacy study
Feighner *et al.*, 1991[287]	Bupropion	Efficacy study
Ferry, 1999[16]	Bupropion	Non-systematic review
Finkel, 1996[288]	Bupropion	Overview of antidepressants
Fiore and Hartman, 1993[289]	NRT	Same as Frazier *et al.*;[105] not a study
Fiore *et al.*, 2000[290]	NRT	Paper based on a full report, see Fiore *et al.*[25]
Fiore *et al.*, 2000[291]	NRT	Not an RCT or safety study
Fortmann *et al.*, 1988[292]	NRT	Efficacy study
Foulds *et al.*, 1993[293]	NRT	Efficacy study
Frenkel *et al.*, 1992[294]	Bupropion	Very general review
Galvin *et al.*, 2001[295]	NRT	Less than 6 months follow-up
Gardner, 1983[296]	Bupropion	Studied only depressed patients intolerant of tricyclic antidepressants
Gariti *et al.*, 2000[297]	NRT	No real data
Gentry *et al.*, 2000[298]	NRT	Not an RCT or an adverse events study

continued

***TABLE 27* contd** *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
George *et al.*, 2000[299]	NRT	Not really NRT; compared two forms of counselling in schizophrenia patients
Girdler *et al.*, 1997[300]	NRT	Not really about NRT but effects of smoking
Glavin *et al.*, 1987[301]	Bupropion	Pharmacology
Glover *et al.*, 1997[302]	NRT	Touched on safety of NRT in patients with chronic obstructive pulmonary disease, but primarily an efficacy study
Goldstein, 1998[303]	Bupropion	Non-systematic review
Gonzales, 2001[304]	Bupropion	Follow-up less than 6 months
Goodnick, 1991[305]	Bupropion	Old efficacy study
Gore and Chien, 1998[306]	NRT	Non-systematic review
Gorman *et al.*, 1997[307]	Neither	Not bupropion or NRT
Gourlay *et al.*, 1995[308]	NRT	Efficacy study
Gourlay and Benowitz, 1996[9]	NRT	Non-systematic review
Grandes *et al.*, 2000[309]	–	Not bupropion or NRT; not an RCT
Grossman *et al.*, 1999[310]	Bupropion	Old efficacy study
Hajek *et al.*, 1988[311]	NRT	Not a safety study
Hajek *et al.*, 1999[312]	NRT	Old efficacy study
Halaris *et al.*, 1983[313]	Bupropion	Antidepressant efficacy study
Hamilton *et al.*, 1983[314]	Bupropion	Pharmacology only
Hamilton *et al.*, 1998[315]	Bupropion	Bupropion just mentioned
Harto Truax *et al.*, 1982[316]	Bupropion	Old efficacy study
Harto Truax *et al.*, 1983[317]	Bupropion	Non-systematic pooling of body weight data from various studies
Hatsukami *et al.*, 2000[318]	NRT	Not concerned with smoking cessation
Haustein, 2000[4]	NRT	Non-systematic review
Hayes and Kristoff, 1986[319]	Bupropion	Non-systematic review
Hays *et al.*, 1999[320]	NRT	Old efficacy study
Hays *et al.*, 1999[321]	NRT	Subset of Jorenby *et al.*, 1995[322]
Hays *et al.*, 2001[323]	Neither	Not about NRT or bupropion
Helge and Denelsky, 2000[324]	Both	Non-systematic review
Henningfield *et al.*, 2000[325]	Neither	Non-systematic review
Herrera *et al.*, 1995[326]	NRT	Primarily an efficacy study
Hilleman *et al.*, 1994[327]	NRT	Efficacy study
Hjalmarson, 1984[328]	NRT	Old efficacy study
Hjalmarson *et al.*, 1994[329]	NRT	Old efficacy study
Hjalmarson *et al.*, 1997[330]	NRT	Old efficacy study
Homsy *et al.*, 1997[331]	NRT	Pharmacokinetics only
Horne *et al.*, 1988[332]	Bupropion	Efficacy study
Hughes *et al.*, 1984[333]	Bupropion	Old efficacy study
Hughes *et al.*, 1989[334]	NRT	Old efficacy study
Hughes, 1993[335]	NRT	Letter (comments)
Hughes, 1993[336]	NRT	Non-systematic review
Hughes *et al.*, 1999[337]	NRT	Old efficacy study
Hurt *et al.*, 1990[338]	–	Efficacy study
Hurt *et al.*, 1994[339]	NRT	Mainly efficacy study
Hurt *et al.*, 1997[52]	Bupropion	Old efficacy study
Hurt *et al.*, 2000[340]	NRT	Efficacy study, but not an RCT

continued

***TABLE 27* contd** *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
Imperial Cancer Research Fund General Practice Research Group, 1993[341]	NRT	Old efficacy study
Jacobsen *et al.*, 1994[342]	Bupropion	Not a relevant population
Jarvis *et al.*, 1982[343]	NRT	Old efficacy study
Jensen *et al.*, 1990[344]	NRT	Mainly an efficacy study
Jimenez Ruiz *et al.*, 1994[345]	NRT	Not a safety study
Jimenez Ruiz *et al.*, 1996[346]	NRT	Old efficacy study; in Spanish
Jimenez Ruiz *et al.*, 1997[347]	NRT	Not primarily an adverse events study
Jimenez Ruiz *et al.*, 1999[348]	NRT	Old efficacy study
Jimenez Ruiz *et al.*, 2000[349]	NRT	Old efficacy study; not an RCT (same study as Jimenez Ruiz *et al.*, 2000[350])
Jimenez Ruiz *et al.*, 2000[350]	NRT	Not an RCT (same study as Jimenez Ruiz *et al.*, 2000[349])
Johnston *et al.*, 1986[351]	Bupropion	Discussion only
Jorenby *et al.*, 1995[322]	NRT	Old efficacy study
Jorenby *et al.*, 1995[352]	NRT	Non-systematic review
Jorenby *et al.*, 1996[353]	NRT	About withdrawal symptoms, not new efficacy or safety data
Jorenby *et al.*, 1999[41]	Bupropion	Old efficacy study
Kalman, 1998[354]	Neither	Non-systematic review; not specifically relevant
Kane *et al.*, 1983[355]	Bupropion	Efficacy study of only 38 patients
Kavoussi *et al.*, 1997[356]	Bupropion	Primarily an efficacy study
Kellner *et al.*, 1994[357]	Bupropion	Did not report an adverse event
Killen *et al.*, 1999[358]	NRT	Not a safety study
Killen *et al.*, 2000[359]	NRT	NRT included in all treatments and therefore not compared with anything
Kinnell, 2001[360]	Bupropion	Letter (comment)
Kirksey *et al.*, 1983[361]	Bupropion	Primarily an efficacy study
Kirksey and Stern, 1984[362]	Bupropion	Title implied a safety and efficacy study, but was primarily an efficacy study and therefore excluded
Kochak *et al.*, 1992[363]	NRT	Subclinical doses used
Kornitzer *et al.*, 1995[364]	NRT	Primarily an efficacy study
Kupecz and Prochazka, 1996[365]	NRT	Efficacy study
Kwan *et al.*, 2001[366]	Bupropion	Not in English
Labbate, 1999[367]	Bupropion	Very brief review
Lagrue *et al.*, 1993[368]	NRT	Letter commenting on a case report
Lancaster and Stead, 2000[14]	NRT	Only one or two relevant studies included; therefore it was decided to use those rather than the review
Lancaster and Stead, 2001[369]	NRT	Included studies of NRT versus NRT plus self-help interventions, but not motivational support
Leigh *et al.*, 2001[370]	NRT	Follow-up less than 6 months
Leischow *et al.*, 1997[371]	NRT	Study of withdrawal symptoms
Levin *et al.*, 1994[372]	NRT	Efficacy study
Lewis *et al.*, 1998[373]	NRT	Primarily an efficacy study
Lineberry *et al.*, 1990[374]	Bupropion	Efficacy study
Lockhart *et al.*, 2000[375]	Neither	About smoking cessation and reducing myocardial infarctions
López-Arrieta *et al.*, 2001[376]	NRT	Indication not relevant
Lumley *et al.*, 2000[377]	NRT	Not NRT or bupropion

continued

***TABLE 27* contd** *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
Margolin *et al.,* 1990[378]	Bupropion	Efficacy study
Margolin *et al.,* 1995[379]	Bupropion	Cocaine dependence
Martin and Robinson, 1995[380]	NRT	Primarily an efficacy study; adverse events reported very briefly
Murray *et al.*, 1996[381]	NRT	An RCT with adverse events described for the treatment arm only; did not distinguish between patch use with and without smoking
Martin *et al.,* 2000[382]	Neither	Description of study
Masco *et al.,* 1994[383]	Bupropion	Old efficacy study
Matsushima *et al.,* 1995[384]	NRT	Animal study
McGovern and Lando, 1992[385]	NRT	Efficacy study
McNabb *et al.,* 1982[386]	NRT	Pharmacokinetics
Mendels *et al.,* 1983[387]	Bupropion	Antidepressant efficacy study
Meredith and Feighner, 1983[388]	Bupropion	Antidepressant efficacy study
Mielke *et al.,* 1997[389]	Neither	Non-systematic review
Mintz *et al.,* 1991[390]	NRT	Primarily interested in effects of alcohol on the effectiveness of NRT gum
Mittman *et al.,* 1999[391]	Bupropion	Not specific to bupropion
Montalto and Garrett, 1998[392]	NRT	Clinical practice exercise paper
Montoya *et al.,* 1996[393]	Bupropion	Small efficacy study
Moxham, 2000[394]	Neither	Editorial comment (background information)
Murray and Anthonisen, 1999[395]	Neither	Non-systematic review
Murray *et al.,* 2000[396]	NRT	NRT was not the main difference between treatments
Namerow *et al.,* 1999[397]	Bupropion	Letter commenting on a case report
NHS CRD, 1998[1]	Neither	Non-systematic review
Norman *et al.,* 1984[398]	Bupropion	General overview of antidepressants
Odishaw and Chen, 2000[399]	Bupropion	Pharmacokinetic drug interaction
O'Hara *et al.,* 1993[400]	NRT	No safety information on NRT
Okuyemi *et al.,* 2000[401]	NRT	Non-systematic review
Oliver, 1993[402]	Bupropion	Overview
Orleans *et al.,* 1994[403]	NRT	Not a safety study
Othmer *et al.,* 1983[404]	Bupropion	Safety not the primary objective
Patel and Greydanus, 2000[405]	–	Non-systematic review
Patten, 2000[406]	NRT	Non-systematic review
Patten *et al.,* 2000[407]	NRT	Follow-up less than 6 months
Pearlstein *et al.,* 1997[408]	Bupropion	Efficacy in premenstrual syndrome
Perkins *et al.,* 1996[409]	NRT	Efficacy study
Perkins, 2001[410]	BOTH	Non-systematic review; useful for background
Perng *et al.,* 1998[33]	NRT	Old efficacy study
Piasecki *et al.,* 1998[411]	NRT	Study of withdrawal patterns
Pickworth *et al.,* 1986[412]	NRT	Pharmacology
Pisinger *et al.,* 1999[3]	NRT	Non-systematic review
Pitts *et al.,* 1983[413]	Bupropion	Antidepressant efficacy study
Preskorn and Othmer, 1984[414]	Bupropion	Non-systematic review
Preskorn, 1995[415]	Bupropion	Source of data for bupropion looked a bit dubious
Ramasubbu, 1999[416]	Neither	Not bupropion or NRT
Raw *et al.,* 1980[417]	NRT	NRT versus psychological therapy, but not an RCT

continued

***TABLE* 27 contd** *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
Reimherr *et al.,* 1998[418]	Bupropion	Primarily an efficacy study
Remick *et al.,* 1982[419]	Bupropion	Not safety
Rennard and Daughton, 2000[420]	Neither	Non-systematic review
Rennard *et al.,* 2001[421]	Bupropion	No results presented
Richmond *et al.,* 1994[422]	NRT	Efficacy study
Richmond, 1997[423]	NRT	Non-systematic review
Richmond, 1999[424]	Neither	Non-systematic review
Riggs *et al.,* 1998[425]	Bupropion	Efficacy in attention deficit hyperactivity disorder
Ritvo *et al.,* 1997[426]	Both	Non-systematic review
Rose *et al.,* 1985[427]	NRT	Efficacy study
Rose *et al.,* 1990[428]	NRT	Efficacy study
Rose and Levin, 1991[429]	Neither	Non-systematic review
Rose *et al.,* 1998[430]	NRT	NRT versus mecamylamine, but only as pre-smoking-cessation treatment
Rose *et al.,* 1999[431]	Neither	Not mecamylamine versus NRT
Rosenstein *et al.,* 1993[432]	Bupropion	Not really about bupropion
Rudorfer *et al.,* 1991[433]	Bupropion	Pharmacology
Rudorfer *et al.,* 1994[434]	Bupropion	Too general
Russell *et al.,* 1993[435]	NRT	Old efficacy study
Sachs *et al.,* 1993[436]	NRT	Old efficacy study
Sachs *et al.,* 1994[437]	Bupropion	Efficacy study
Saenghirunvattana, 1995[438]	NRT	Efficacy study
Salin-Pascual *et al.,* 1995[439]	NRT	Effects of nicotine on sleep in patients with depression; not really an adverse events or safety study
Salvador Llivina *et al.,* 1988[440]	NRT	Old efficacy study
Sampablo Lauro *et al.,* 2000[441]	NRT	Efficacy study
Sarko, 2000[442]	Bupropion	Too general
Sawe, 1997[443]	NRT	Just a short version of details in the CEASE trial full publication, which is an efficacy study[121]
Schneider *et al.,* 1995[444]	NRT	Old efficacy study
Schneider *et al.,* 1996[445]	NRT	Old efficacy study
Selby *et al.,* 2001[446]	Bupropion	Follow-up less than 6 months
Semenchuk and Davis, 2000[447]	Bupropion	Efficacy of bupropion in neuropathic pain
Settle, 1998[448]	Bupropion	Non-systematic review of the side-effect profile of bupropion
Settle *et al.,* 1999[449]	Bupropion	Excluded as no real explanation was given for selecting the three studies for pooling
Shaw *et al.,* 1998[450]	NRT	Not a safety study
Shiffman *et al.,* 2000[451]	NRT	Outcome effect on morning craving; follow-up less than 6 months
Shiffman *et al.,* 2000[452]	NRT	Follow-up less than 6 months
Shopsin *et al.,* 1983[453]	Bupropion	Old efficacy study
Shuster, 1997[454]	NRT	Not an original article
Shuster, 1997[455]	NRT	Not an original article (newspaper-type report)
Silagy and Stead, 2001[456]	Neither	Not relevant to NRT or bupropion
Silver *et al.,* 1996[457]	NRT	Efficacy with neuroleptic agents in Tourette's syndrome
Sinusas and Coroso, 1993[458]	NRT	Old efficacy study
Sivyer *et al.,* 1994[459]	NRT	Efficacy study

continued

***TABLE 27* contd** *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
Skaar *et al.,* 1997[6]	Neither	Non-systematic review
Smith *et al.,* 1992[460]	NRT	A non-systematic review of skin reactions and causes
Smith *et al.,* 1995[461]	NRT	Old efficacy study
Smith *et al.,* 1996[462]	NRT	Primarily an efficacy study
Sonderskov *et al.,* 1997[463]	NRT	Primarily an efficacy study
Spencer *et al.,* 1993[464]	Bupropion	Population not relevant
Spiller *et al.,* 1994[465]	Bupropion	Bupropion overdose (not really applicable to normal use of drug)
Stapleton *et al.,* 1995[202]	NRT	Old efficacy study
Stead and Lancaster, 2001[466]	Neither	Not relevant
Stern *et al.,* 1982[467]	Bupropion	Two studies, both on efficacy
Stoll *et al.,* 1994[468]	Bupropion	Not really about effects of bupropion
Strecher, 1999[469]	Neither	Not about bupropion or NRT
Sudan, 1994[470]	NRT	Discussion paper
Sudan, 1995[471]	NRT	Discussion paper
Sutherland *et al.,* 1992[472]	NRT	Old efficacy study
Tennstedt and Lachapelle, 1998[473]	NRT	Review of transdermal preparations, not specifically NRT; in French
Thomas *et al.,* 1995[474]	NRT	Efficacy in ulcerative colitis
Thompson and Hunter, 1998[8]	NRT	Non-systematic review
Thorton, 1986[475]	NRT	No results given
Thorsteinsson *et al.,* 2001[476]	NRT	Follow-up period too short
Tonnesen *et al.,* 1988[477]	NRT	Efficacy study
Tonnesen *et al.,* 1991[478]	NRT	Old efficacy study; safety not really a primary objective
Tonnesen *et al.,* 1992[479]	NRT	Mainly an efficacy study
Tonnesen *et al.,* 1993[480]	NRT	Old efficacy study
Tonnesen *et al.,* 1993[481]	NRT	Old efficacy study
Tonnesen *et al.,* 1996[482]	NRT	Efficacy study
Tonnesen *et al.,* 1999[121]	NRT	Efficacy study
Tonnesen, 1999[483]	NRT	Non-systematic review
Tonnesen and Mikkelsen, 2000[36]	NRT	In 2001 update of Silagy (Cochrane Review of NRT)[26]
Toral *et al.,* 1998[484]	NRT	Efficacy study; in Spanish
Transdermal Nicotine Study Group, 1991[485]	NRT	Efficacy study
Trappler and Miyashiro, 2000[486]	Bupropion	Report of a possible drug interaction (with amantadine)
Tsoh *et al.,* 1997[487]	Neither	Non-systematic review
Tsoh *et al.,* 2000[488]	Neither	Study of incidence of depression after attempting to stop smoking
Tucker, 1983[489]	Bupropion	Preclinical safety
van den Berkmortel *et al.,* 2000[490]	Neither	Non-systematic review
van der Klauw and Stricker, 1994[491]	NRT	In Dutch
van Ree, 1984[492]	NRT	Efficacy study; not in English
Vida and Looper, 1999[493]	Bupropion	Methodology paper about how to compare the rates of adverse events in different trials on different drugs; no raw data
Vieregge *et al.,* 2000[494]	NRT	Follow-up less than 6 months
Vleggaar *et al.,* 2000[495]	NRT	Study of efficacy in sclerosing cholangitis
Wallstrom *et al.,* 2000[496]	NRT	Included in the latest update of the Cochrane Review of NRT (3rd edition, 2001)[26]

continued

***TABLE* 27 contd** *Excluded studies*

Reference	Bupropion or NRT	Reason for exclusion*
Walsh, 1994[497]	Neither	Excluded from review but used as background on adverse effects of smoking in pregnancy
Wadland *et al.*, 2001[498]	NRT	Study of efficacy of telephone counselling when used in addition to usual care (mainly, but not exclusively, NRT patches)
Weihs *et al.*, 2000[499]	Bupropion	Efficacy study
Weiner *et al.*, 2001[500]	Bupropion	Not an RCT or a safety study
Weisler *et al.*, 1994[501]	Bupropion	Efficacy study
Wenger and Stern, 1983[130]	Bupropion	Non-systematic review
West and Willis, 1998[502]	NRT	Comparison with dextrose but follow-up period too short (< 6 months)
West *et al.*, 2000[503]	NRT	Follow-up less than 6 months
Westman *et al.*, 1993[504]	NRT	Efficacy study
Westman *et al.*, 1995[505]	NRT	Efficacy study
Wewers, 1999[506]	Neither	Non-systematic review
White and Andrews, 1999[507]	Bupropion	Description of data collection, but no data given
Whiteman *et al.*, 1982[508]	Bupropion	Efficacy in depression
Wilson *et al.*, 1995[509]	NRT	Efficacy in Alzheimer's disease
Wilson *et al.*, 2000[510]	–	Not about intervention
Wolf *et al.*, 1998[511]	NRT	Non-systematic review of skin reactions to NRT patches
Wong *et al.*, 1999[512]	NRT	Effects on gastric emptying
Wongwiwatthananukit *et al.*, 1998[513]	Both	Non-systematic review
Zajecka, 2001[514]	Bupropion	Non-systematic review
Zhu *et al.*, 2000[515]	NRT	Not an RCT or a safety study; not really about NRT
Zobrist *et al.*, 1996[516]	NRT	Pharmacokinetics
Zobrist *et al.*, 1998[517]	NRT	Mainly an efficacy study
Zung *et al.*, 1983[518]	Bupropion	Efficacy study

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

Appendix 3

Data extraction forms

Systematic reviews

Data were 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 (study design, participant details, intervention, outcomes)
  - exclusion criteria
  - how the quality of studies was assessed
  - number of studies included
  - types of studies and number included (RCTs, quasi-RCTs, controlled trials, other)
  - participants included in review (type of smokers, proportion of men and women, level of nicotine dependence, Fagerstrom score)
  - specific intervention
  - specific comparator
  - definition of smoking cessation
  - duration of follow-up
  - setting (hospital, general practice, smoking clinic, other)
  - participants actually included
  - outcome measure(s) (description, including definition of smoking cessation used (point prevalence, sustained abstinence, other))
  - quality of studies
  - comments.
- Results of review:
  - comparison (description, including which intervention(s) versus which comparators, nature of subgroup if any)
  - number of studies included in the comparison
  - comments on the design and quality of studies included in the comparison
  - pooled OR or relative risk with the 95% CI for comparison 1
  - other result(s) for comparison 1
  - comment on result of comparison 1
  - repeat above points for all comparisons.

Effectiveness data

Effectiveness data were extracted from newly identified RCTs only and entered into an Access database under the headings listed below. The data do 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 or IV; not stated)
  - level of randomisation (patient or therapist)
  - length of follow-up period
  - number and times of follow-up measurements
  - outcome measures
  - definition of smoking cessation used
  - method of assessment of smoking cessation
  - Intention-to-treat analysis performed (yes, no, not stated, unclear)
  - per protocol analysis performed (yes, no, not stated, unclear)
  - participant details
  - specific intervention(s)
  - specific comparator(s)
  - number of participants recruited and attrition.
- Study quality:
  - checklist given in appendix 4.
- Results:
  - percentage not smoking at 3, 6 and 12 months with intervention and comparator
  - result for comparison (OR with 95% CI).

Adverse events data

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

- nature of data (adverse events 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 study
- specific intervention
- specific comparator
- duration of therapy
- duration of follow-up
- participant details
- list of all adverse events associated with intervention
- proportion of participants experiencing any adverse event
- clinical significance of this adverse event
- comments on the adverse event
- repeat for all adverse events reported.

Economic evaluations

The data extraction sheet for economic-evaluation studies of smoking-cessation interventions is reproduced on pages 111–113.

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 quitters (3) Life-years saved

   (4) QALYs saved (5) Other: _____

5. How was the 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) Life-years or QALYs from the 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/1000	No. of quitters per 1000	Life-years saved per 1000	QALYs saved per 1000
1.				
2.				
3.				
4.				

(2) Incremental analysis

(Reference intervention: _____)

Intervention	Costs per quitter	Costs per death prevented	Costs per life-year saved	Costs per QALY
1.				
2.				
3.				
4.				

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

Appendix 4

Quality assessment criteria

In the following checklists, items were graded in terms of 'yes' (item properly addressed); 'no' (item not properly addressed); or 'unclear', 'not enough information' or 'not applicable'.

Systematic reviews

The quality of systematic reviews was assessed using a checklist based on the following criteria (based on the *Manual for Selecting Reviews and Writing Abstracts for DARE*[19]):

- Do the inclusion/exclusion criteria for the inclusion of studies in the review 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

RCTs of effectiveness were assessed using the following criteria (based on CRD Report No. 4[20]):

- 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, while 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, and 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 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?

Adverse events studies

Studies of adverse events were assessed using the following criteria.

Systematic reviews and RCTs

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

Cohort studies and uncontrolled studies

Cohort studies and all uncontrolled studies were assessed according to the following criteria (based on the checklists given by Crombie[21]). 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

Case–control studies were assessed according to the following criteria (based on the checklists given by Crombie[21]):

- 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

Survey-type studies were be assessed according to the following criteria (based on the checklists given by Crombie[21]):

- 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

Surveillance data/databases were assessed according to the following criteria:

- 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?

Appendix 5

Data extraction tables: clinical effectiveness

TABLE 28 *Clinical effectiveness of NRT: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Clavel-Chapelon *et al.*, 1997[28] ***Design*** 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 criteria*** Inclusions: age ≥ 18 years; smoked at least 10 cigarettes/day Exclusions: history of gastric ulcer; coronary heart disease; 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 time smoking: 18 ± 9 years Previous quit attempt: 81% ***Participant numbers and attrition*** Total, *n* = 996 Gum + acupuncture, *n* = 268 Gum + placebo acupuncture, *n* = 213 Placebo gum + acupuncture, *n* = 272 Placebo gum + placebo acupuncture, *n* = 243 Two participants lost to follow-up after 9 months of study, but intention-to-treat analysis was undertaken	***Specific intervention*** Nicotine gum 2 mg (*ad libitum* up to 30 pieces/day during the first 6 months) + acupuncture (days 0, 7 and 28 of study) Nicotine gum 2 mg (*ad libitum* up to 30 pieces/day during the first 6 months) + placebo acupuncture (days 0, 7 and 28 of study) ***Comparator*** Placebo gum + placebo acupuncture Placebo gum + acupuncture (days 0, 7 and 28 of study)	***Outcome*** Sustained abstinence ***% intervention group not smoking*** At 3 months: gum + acupuncture, 26.5 (95% CI, 21.2 to 31.8); gum + placebo acupuncture, 25.8 (95% CI, 19.9 to 31.7) At 12 months: gum + acupuncture, 11.2 (95% CI, 8.0 to 15.5); gum + placebo acupuncture, 10.9 (95% CI, 7.4 to 15.9) At > 12 months: gum + acupuncture, 6.1 (95% CI, 3.7 to 9.9); gum + placebo acupuncture, 6.2 (95% CI, 3.2 to 11.8) ***% comparator group not smoking*** At 3 months: placebo gum + placebo acupuncture, 17.7 (95% CI, 13.2 to 22.2); placebo gum + acupuncture, 20.6 (95% CI, 15.5 to 25.7) At 12 months: placebo gum + placebo acupuncture, 6.5 (95% CI, 4.1 to 10.1); placebo gum + acupuncture, 10.3 (95% CI, 7.1 to 14.7) At > 12 months: placebo gum + placebo acupuncture, 5.1 (95% CI, 3.0 to 8.5); placebo gum + acupuncture, 7.3 (95% CI, 4.5 to 11.6) ***OR for comparison*** None reported	Log-rank test NS for difference between treatments

continued

***TABLE 28* contd** *Clinical effectiveness of NRT: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Jensen *et al.*, 1991[27] ***Design*** Unblinded, parallel group ***Schedule of study visits*** Eight 2-hour visits to the clinic (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 > 4 ppm) at any study visit was not allowed to continue in the study (it was assumed they were counted as treatment failures) ***Method*** CO measurement (Ecolyser carbon monoxide monitor)	***Inclusion/exclusion criteria*** Inclusions: smoked > 10 cigarettes/day for > 10 years Exclusions: drug or alcohol misuse; psychiatric problems; cardiovascular disease; pregnant women ***Baseline characteristics*** Mean ± SD age: 42.1 ± 12.2 years Men/women: 219/491 Mean ± SD age started smoking: 14.8 ± 2.4 years Mean ± SD cigarette consumption: 21.7 ± 9.1 cigarettes/day 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 3 months ***Comparator*** Silver acetate gum or ordinary chewing gum used for 3 months	***Outcome*** 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% ***OR for comparison*** None reported	No statistically significant difference between treatments for abstinence at 6 months

continued

***TABLE 28* contd** *Clinical effectiveness of NRT: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Wong *et al.*, 1999[29] ***Design*** 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 6 months after randomisation ***Outcome measures*** Smoking cessation ***Definition of smoking cessation*** 1-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 8 ppm or less); continued abstinence defined as no evidence of smoking	***Inclusion/exclusion criteria*** Inclusions: age 18–65 years, smoked ≥ 10 cigarettes/day for the past year, baseline CO ≥ 15 ppm, in good general health Exclusions: use of medication contraindicated with NRT or naltrexone; weight < 100 lb; drug or alcohol abuse; history of depression or other psychiatric disorder requiring medication; cardiovascular, cerebral, respiratory, hepatic, renal or gastrointestinal condition or other systemic disease, including cancer; women who were pregnant or at risk of becoming pregnant ***Baseline characteristics*** Mean ± SD age: 42.1 ± 10.9 years Sex: 53% women Mean ± SD cigarette consumption: 27.8 ± 11.8 cigarettes/day Mean ± time of smoking: 24.5 ± 10.6 years Mean ± SD Fagerstrom score: 7.0 ± 1.8 Mean ± SD baseline CO level: 37.5 ± 15.2 ppm ***Participant numbers and attrition*** Total, *n* = 100 Patch + naltrexone, *n* = 26 Patch + placebo, *n* = 25 Naltrexone alone, *n* = 23 Placebo alone, *n* = 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) + naltrexone 50 mg/day ***Comparator*** Naltrexone 50 mg/day tablet Placebo	***Outcome*** Sustained abstinence ***% intervention group not smoking*** At 6 months: patch + placebo, 28%; patch + naltrexone, 27% ***% comparator group not smoking*** At 6 months: naltrexone only, 9%; placebo only, 8% ***OR for comparison*** Patch vs no treatment, 4.26 (95% CI, 1.29 to 14.05); 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; 1 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 $p = 0.007$)

continued

***TABLE 28* contd** *Clinical effectiveness of NRT: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Wisborg *et al.*, 2000[31] ***Design*** Double-blind, parallel group ***Schedule of study visits*** Initial visit prior to week 22 of pregnancy; second and third visits at 8 and 11 weeks after the first visit; 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 < 26 ng/ml at the fourth visit	***Inclusion/exclusion criteria*** Inclusions: healthy pregnant women who smoked ≥ 10 cigarettes/day and were < 22 weeks pregnant ***Baseline characteristics*** Mean age: 28 years Mean ± SD cigarette consumption: nicotine group, 13.4 ± 4.0 cigarettes/day; placebo group, 14.2 ± 4.4 cigarettes/day ***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 (fourth prenatal visit), 28%; at 12 months (3 months post-partum), 21%; at > 12 months (12 months post-partum), 15% ***% comparator group not smoking*** At 6 months (fourth prenatal visit), 25%; at 12 months (3 months post-partum), 18%; at > 12 months (12 months post-partum), 14% ***OR 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 There was no statistically significant difference between the treatment groups for any assessment of smoking cessation

continued

***TABLE 28* contd** *Clinical effectiveness of NRT: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Solomon *et al.*, 2000[30] ***Design*** Unblinded, parallel group ***Schedule of study visits*** Assessments (all conducted by telephone) at baseline, 10 days and 3 and 6 months after enrolment ***Outcome measures*** Smoking cessation ***Definition of smoking cessation*** Point prevalence (i.e. no smoking in the previous 7 days) ***Method*** Self-report, confirmed by CO readings in about 60% of reportedly abstinent patients	***Inclusion/exclusion criteria*** Inclusions: age 18–50 years; smoked 4 cigarettes/day; highly motivated to try quitting smoking; not currently using NRT; no contraindications to the use of nicotine patches; not pregnant or breast-feeding, or planning pregnancy in the next 3 months; low income; other criteria pertinent to the local conduct of the study ***Baseline characteristics*** Mean ± SD age: 33 ± 8.5 years Mean ± SD cigarette consumption: 23.7 ± 11.8 cigarettes/day ***Participant numbers and attrition*** Total, *n* = 214 Withdrawals: 5 (two lived in the same household; one became pregnant; two died)	***Specific intervention*** Free nicotine patches (patients smoking > 10 cigarettes/day, 6 weeks of 21 mg, 2 weeks of 14 mg and 2 weeks 7 mg patches; patients smoking 5–10 cigarettes/day, 6 weeks of 14 mg, 2 weeks of 7 mg patches) + proactive telephone support approximately biweekly for 3 months ***Comparator*** Free nicotine patches (patients smoking > 10 cigarettes/day, 6 weeks of 21 mg, 2 weeks of 14 mg and 2 weeks of 7 mg patches; patients smoking 5–10 cigarettes/day, 6 weeks of 14 mg, 2 weeks of 7 mg patches) only	***Outcome*** Point prevalence ***% intervention group not smoking*** At 3 months, 42%; at 6 months, 23% (20% abstinent at 3 and 6 months) ***% comparator group not smoking*** At 3 months, 28%; at 6 months, 19% (15% abstinent at both 3 and 6 months) ***OR for comparison*** Not reported	Difference between reported abstinence at 3 months was greater with patch + telephone support compared to patch alone (p = 0.03), but not at 6 months (NS) nor for the percentage of quitters at both 3 and 6 months (NS)

continued

***TABLE 28* contd** *Clinical effectiveness of NRT: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors GlaxoSmithKline, 2000[32*] ***Design*** Double-blind, parallel group ***Schedule of study visits*** Baseline, follow-up (1, 2, 4, 6 and 12 weeks, and 6 and 12 months) ***Outcome measures*** Primary outcome was smoking cessation at 6 weeks; other outcome measures included smoking cessation at 3, 6 and 12 months, changes in body weight, withdrawal and craving, and adverse events ***Definition of smoking cessation*** Abstinence from smoking from week 2 to the follow-up point ***Method*** Patient self-report, verified by exhaled CO levels	***Inclusion/exclusion criteria*** – ***Baseline characteristics*** – ***Participant numbers and attrition*** –	***Specific intervention*** 2 mg nicotine polacrilex oral lozenge and 4 mg nicotine polacrilex oral lozenge for 6 months ***Comparator*** 2 mg and 4 mg placebo lozenges	***Outcome*** Sustained abstinence	

continued

***TABLE 28* contd** *Clinical effectiveness of NRT: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors GlaxoSmithKline, 1999[33*] ***Design*** Unblinded, parallel group ***Schedule of study visits*** Baseline, weekly visits during the treatment phase (13 weeks) and follow-up evaluations at 6 and 12 months ***Outcome measures*** Primary outcome was continuous abstinence from smoking for a 4-week period beginning with week 4 and continuing to the end of week 7; weekly point prevalence was abstinence from day 22, change from baseline number of cigarettes per day, severity of nicotine withdrawal symptoms ***Definition of smoking cessation*** Point prevalence defined as continuous abstinence for a 7-day period during the treatment period and throughout the 6-month and 1-year follow-ups ***Method*** Self-report of not smoking (0 cigarettes/day), confirmed by CO level ≤ 10 ppm	***Inclusion/exclusion criteria*** – ***Baseline characteristics*** – ***Participant numbers and attrition*** –	***Specific intervention*** – ***Comparator*** –	***Outcome*** Point prevalence	Results reported individually by centre. Six-month data were those reported at week 26

CO, carbon monoxide; NS, not significant

[*] *The data for this study were supplied by the manufacturer and have been removed from this publication for reasons of commercial confidentiality*

TABLE 29 *Clinical effectiveness of bupropion: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors GlaxoSmithKline, 1999[43] *	***Inclusion/exclusion criteria*** –	***Specific intervention*** Bupropion hydrochloride SR (150 mg b.i.d.) for 7 weeks	***Outcome 1*** Sustained abstinence	
Design Double-blind, parallel group	***Baseline characteristics*** –	***Comparator*** Placebo	***Outcome 2*** Point prevalence	
Schedule of study visits Baseline, treatment visits (up to 7 weeks), monthly follow-up visits from weeks 7 to 52	***Participant numbers and attrition*** –			
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 Self-report, confirmed by exhaled CO < 10 ppm				

continued

***TABLE 29* contd** *Clinical effectiveness of bupropion: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors GlaxoSmithKline, 1999[33]*	***Inclusion/exclusion criteria*** –	***Specific intervention*** –	***Outcome*** Point prevalence	Six-month data was that reported at week 26
Design Unblinded, parallel group	***Baseline characteristics*** –	***Comparator*** –		
Schedule of study visits Baseline, weekly visits during the treatment phase (13 weeks), follow-up evaluations at 6 and 12 months	***Participant numbers and attrition*** –			
Outcome measures Primary outcome was continuous smoking abstinence for a 4-week period beginning with week 4 and continuing to the end of week 7. Weekly point prevalence was abstinence from day 22, a change from the baseline number of cigarettes per day, severity of nicotine withdrawal symptoms				
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 Self-report of not smoking (0 cigarettes/day) comfirmed by a CO level ≤ 10 ppm				

continued

***TABLE 29* contd** *Clinical effectiveness of bupropion: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors GlaxoSmithKline, 2000[34] *	***Inclusion/exclusion criteria*** –	***Specific intervention*** Bupropion hydrochloride SR (150 mg b.i.d.)	***Outcome 1*** Sustained abstinence	
Design Double-blind, parallel group	***Baseline characteristics*** –	***Comparator*** Placebo		
Schedule of study visits Baseline visit, six treatment visits, follow-up visits at weeks 12, 26 and 52	***Participant numbers and attrition*** –			
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 at 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 Self-report confirmed by exhaled CO < 10 ppm				

continued

***TABLE 29* contd** *Clinical effectiveness of bupropion: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Gonzalez *et al.*, 2001[49] ***Design*** 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*** Self-report confirmed by exhaled CO of < 10 ppm	***Inclusion/exclusion criteria*** Inclusions: had taken and tolerated a 2-week (or longer) course of bupropion for smoking cessation; age ≥ 18 years; average consumption ≥ 15 cigarettes/day during the preceding month; had not quit for > 24 hours in preceding month; motivated to quit smoking Exclusions: 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, psychosis or bipolar disorder; history of alcohol or substance abuse other than cigarette smoking; allergy or sensitivity to bupropion; use of psychoactive drug within preceding week; using medications that lower seizure threshold; use of another investigational drug in preceding 4 weeks; using other smoking-cessation treatments; using other tobacco products; other household members participating in the study or another clinical study; had a problem that would affect study compliance; presence of a 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 Withdrawals: 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, 150 mg b.i.d. for 12 weeks) ***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 not included in this report due to commercial confidentiality

continued

***TABLE 29* contd** *Clinical effectiveness of bupropion: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Herzberg *et al.*, 2001[53] ***Design*** 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 ≤ 10 ppm at each study visit	***Inclusion/exclusion criteria*** 15 patients from a Veterans Medical Affairs Center who expressed a desire to stop smoking; either receiving no psychotrophic medication or a stable psychotrophic regimen (same dosage and drug for at least 6 months before the study); met DSM-IV criteria for a primary diagnosis of post-traumatic stress disorder ***Baseline characteristics*** Mean (range) age: 50 (47–58) years Mean (range) pack-year history: 57 (21–203) Mean (range) cigarette consumption: 33 (15–99) cigarettes/day Heavy smokers (> 25 cigarettes/day): 7/15 ***Participant numbers and attrition*** Total, *n* = 15 Bupropion SR, *n* = 10, Placebo, *n* = 5 7/15 did not complete the 12-week treatment: 6 started smoking again (2/10 on bupropion, 4/5 on placebo); 1 bupropion patient withdrew due to adverse effects	***Specific intervention*** Bupropion SR (150 mg for 3–4 days, then 150 mg b.i.d.) ***Comparator*** Placebo	***Outcome*** Sustained abstinence ***% intervention group not smoking*** At 3 months (12 weeks), 60%; at 6 months, 40% ***% comparator group not smoking*** At 3 months (12 weeks), 20%; at 6 months, not stated ***OR for comparison*** None reported	

continued

***TABLE 29* contd** *Clinical effectiveness of bupropion: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors Tashkin *et al.*, 2001;[47] GlaxoSmithKline, 2000[46] ***Design*** Double-blind, parallel group ***Schedule of study visits*** 4, 7 and 12 weeks, and 6 months ***Outcome measures*** Primary outcome was continuous abstinence for 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*** Self-report of 0 cigarettes/day confirmed by exhaled CO values of ≤ 10 ppm	***Inclusion/exclusion criteria*** Inclusions: current smokers with stage I or II chronic obstructive airways disease; age ≥ 35 years; smoked ≥ 15 cigarettes/day for the previous year; had not stopped smoking for more than 3 months in the previous year; motivated to stop smoking Exclusions: any serious or unstable medical disorders that might affect lung function or for which bupropion SR was contraindicated; current diagnosis of major depression ***Baseline characteristics*** (Bupropion SR; placebo) Men/women: bupropion, 113/206 (55%); placebo, 113/205 (55%) Mean ± SD age: bupropion, 53.2 ± 9.0 years; placebo, 54.5 ± 9.5 years Mean ± SD consumption: bupropion, 28.7 ± 11.1 cigarettes/day; placebo, 27.6 ± 10.2 cigarettes/day Mean ± SD pack-year history: bupropion, 52.6 ± 25.8 years; placebo, 51.4 ± 23.8 Mean ± SD age when started smoking: bupropion, 16.5 ± 3.5 years; placebo, 17.3 ± 4.1 years Mean ± SD Fagerstrom score: bupropion, 7.1 ± 1.7; placebo, 7.0 ± 1.7 ***Participant numbers and attrition*** Total, *n* = 404 Bupropion SR, *n* = 204 Placebo, *n* = 200 Withdrawals at 6months: bupropion SR, *n* = 129; placebo, *n* = 149	***Specific intervention*** Bupropion SR (150 mg/day for days 1–3, 150 mg b.i.d. for days 4–84) ***Comparator*** Placebo	***Outcome 1*** Sustained abstinence ***% intervention group not smoking*** At 3 months (12 weeks), 18% (36/204); at 6 months, 16% (32/204) ***% comparator group not smoking*** At 3 months (12 weeks), 10% (20/200); at 6 months, 9% (18/200) ***OR 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

continued

***TABLE 29* contd** *Clinical effectiveness of bupropion: newly identified RCTs*

Study details	Participant details	Intervention details	Results	Comments
Authors GlaxoSmithKline, 1999[44] *	***Inclusion/exclusion criteria*** To enter the RCT part of the study, an participants had to have completed an open 7-week treatment period on bupropion and to have achieved abstinence	***Specific intervention*** Bupropion SR 300 mg/day	***Outcome*** Sustained abstinence	
Design Double-blind, parallel group	***Baseline characteristics*** –	***Comparator*** Placebo		
Schedule of study visits Baseline visit, treatment visits (up to week 7), follow-up visits (weeks 12, 24, 36, 52 and 56 and months 15, 18 and 24)	***Participant numbers and attrition*** –			
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 Self-report confirmed by exhaled CO levels of < 10 ppm; if the self-report did not match the exhaled CO findings, the participant was assumed to have relapsed				

b.d., twice daily

[*] *The data for this study were supplied by the manufacturer and have been removed from this publication for reasons of commercial confidentiality*

TABLE 30 *Clinical effectiveness of NRT: systematic reviews*[*]

Review details
Author: Silagy *et al.*, 2001[26]

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 different 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 and/or initial level of nicotine dependency. Studies which randomised therapists, rather than smokers, to offer NRT or a control were included, providing that the specific aim of the study was to examine the effect of NRT on smoking cessation. Trials that randomised physicians 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 prevalence 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 a 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

Male/female ratio: Not stated

Level of nicotine dependence: Any

Fagerstrom score: Whole range 0–11. Smokers with a score of < 7 were classed as 'low' dependency, and those with a score ≥ 7 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 the systematic review); nicotine inhalers/inhalators (details not given in the systematic review); and nicotine tablets (details not given in the systematic review). 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 the initial consultation or the number of further assessments or visits exceeded two, this was classed as 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 prevalence, 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 CO in expired air was the most common form of validation used. However, the cut-off level of CO used to define abstinence varied from less than 4 ppm to 11 ppm. In one trial participants who smoked up to three cigarettes/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 workplace settings, two in a university clinic and one in a Veterans Affairs Medical Center. Eight studies were in specialised smoking-cessation clinics and seven trials were in hospitals (i.e. patients, usually with a smoking-related illness). Three studies were of over-the-counter NRT. The remaining trials were in participants from the community, most of whom had been recruited in response to media advertisements, but who were treated in clinics

continued

***TABLE 30* contd** *Clinical effectiveness of NRT: systematic reviews*[*]

***Results* contd**

Participants: All trials, except for two, included both male and female participants. Kornitzer and co-workers, 1987 included only men and Pirie and co-workers, 1992 included only women. The range of the mean number of cigarettes smoked (per day) by participants in those studies included in the review which provided this data was 15.5–32.9. One study included only relapsed smokers (Gourlay and co-workers, 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 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 and co-workers, 1986; Richmond and Heather, 1990; Richmond *et al*., 1990; Russell and co-workers, 1983), birth date (Fagerstrom, 1984), or smoker's clinic group (McGovern and Lando, 1992)

Comments

Combination therapy was not the main focus of review. With the exception of 12 gum trials and 13 patch trials, participants were followed for at least 12 months

[*] *For specific studies mentioned in this table, see appendix 12*

TABLE 31 *Clinical effectiveness of bupropion: systematic reviews*[*]

Review details
Author: Hughes and Stead, 2000[42]

Objective: To assess the effectiveness of antidepressant medications in aiding long-term smoking cessation. Bupropion is one of the drugs included in this systematic review

Inclusion criteria: –

Study design: RCTs. 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 6 months follow-up were excluded from the review

Quality assessment: According to method of randomisation, the definition of abstinence and whether biochemical validation was used. Classification A to D (A, appropriate method of randomisation with proper 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

Male/female ratio: Not stated for review overall

Level of nicotine dependence: Not stated

Fagerstrom score: Not stated. See comments (below) for more information on level of nicotine dependence

Specific intervention: Bupropion standard release and SR, 100–300 mg/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 and co-workers, 1992) which reported abstinence (definition not stated) at 6 months and another that reported continuous abstinence at 2 years (1 year after the end of treatment) (Hays and co-workers, 2000). Two of the studies that reported continued abstinence at 12 months defined this as continuous abstinence from day 22 or day 29 to 12 months (Hurt and co-workers, 1997 and Ferry and Burchette, 1994, respectively)

Duration of follow-up: 6–24 months

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

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

Quality of included studies: The quality ratings of the studies included in the systematic review are: Ferry and co-workers, 1992, B; Ferry and Burchette, 1994, B; Hurt and co-workers, 1997, B; Jorenby and co-workers, 1999, B; Hays and co-workers, 2000, B

Comments
Although this systematic review 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 antidepressant were analysed separately. Therefore, only information pertaining to bupropion were 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 systematic review. In these three studies the average number of cigarettes smoked per day ranged from 25 to 46

[*] *For specific studies mentioned in this table, see appendix 12*

Appendix 6

Data extraction tables: adverse events with NRT

TABLE 32 *Adverse events with NRT reported in RCTs: cardiovascular events (healthy subjects)*

Study details	Participant details	Results	Comments
Authors Fishbein *et al.*, 2000[56] ***Study design*** RCT ***Specific intervention*** Nicotol NS (3 mg administered as three 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 after administration	***Number of participants*** Intervention: *n* = 10 Comparator: *n* = 10 ***Inclusion/exclusion criteria*** Inclusions: male and female first-year medical students aged 21–29 years; participants had to have abstained from all nicotine-containing products for at least 1 month before the study Exclusions: pregnancy and breast-feeding, allergy to nicotine, use of medicine or caffeine within 12 h before study, presence of hypertension, diabetes or other chronic diseases ***Baseline characteristics*** Mean ± SD age: nicotine, 23.7 ± 2.2 years; placebo, 22.8 ± 1.1 years ***Proportion of participants reporting an adverse event*** Intervention: NA Comparator: NA	***Intervention*** **List of adverse events**: looked at biochemical and clinical effects over a short period. Peak ± SD change from baseline SBP 7.13 ± 9.42% (p = 0.03 compared with placebo). Mean peak SBP ± SD 5 min after NRT administration, 135.4 ± 12.30) mmHg. No statistically significant difference in DBP or heart rate 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**: NA ***Comparator*** **List of adverse events**: looked at biochemical and clinical effects over a short period. Peak ± SD change from baseline SBP, –1.61 ± 7.26% **Comments**: NA	Participants were randomised in a double-blind manner, blocking on gender. However, 14/20 participants correctly identified their intervention assignment
Authors Allen *et al.*, 1995[60] ***Study design*** RCT ***Specific intervention*** 2 mg nicotine gum ***Comparator*** Placebo ***Duration of therapy*** 8 weeks ***Duration of follow-up*** Tests conducted at baseline, 4 weeks and 8 weeks	***Number of participants*** Intervention: *n* = 22, abstainers who used the 2 mg gum Comparator: *n* = 34, abstainers who were given placebo ***Inclusion/exclusion*** Inclusions: users of smokeless tobacco. Study focused on those who abstained from tobacco use ***Baseline characteristics*** Mean ± SD age: 34.1 ± 10.3 years Sex: 100% male ***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**: no change in the mean values for SBP, DBP, heart rate, total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides was 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, heart rate, total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides was seen from baseline to either time point in the study	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 and < 100 mmHg) at baseline did not have reduced blood pressure at 8 weeks

continued

***TABLE 32* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (healthy subjects)*

Study details	Participant details	Results	Comments
Authors Khoury *et al.*, 1996[64] ***Study design*** RCT ***Specific intervention*** Transdermal nicotine patches (14 mg/day for Fagestrom score of 5 or 6, 21 mg/day for Fagestrom score of 7 or more) ***Comparator*** Placebo containing 13% of nicotine of treatment ***Duration of therapy*** 2 weeks ***Duration of follow-up*** Concurrent with duration of study	***Number of participants*** Intervention: *n* = 25 Comparator: *n* = 25 ***Inclusion/exclusion criteria*** Inclusions: healthy smokers, motivated to quit; all participants received psychological support; evidence of dependence on smoking as indicated by a Fagestrom score of ≥ 5 Exclusions: 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 (e.g. history of myocardial infarction, angina pectoris, valvular disease, positive exercise test), subjects exhibiting a resting heart rate > 110 beats/min, abnormal ECG at rest, DBP > 95 mmHg, SBP > 180 mmHg, episodes of ST-segment depression or presence of complex ventricular arrhythmias during the screening Holter monitoring ***Participant characteristics*** Mean age: treatment, 42.5 years; placebo, 40.6 years Sex: treatment, 13/25 male; placebo 13/25 male Mean No. of smoking years: treatment, 24.3; placebo, 22.4 Fagestrom score 5–6: treatment, 9; placebo, 7 Fagestrom score 7–11: treatment, 13; placebo, 15 Mean CO reading at baseline: treatment, 14.2 ppm; placebo, 13.2 ppm Mean urine cotinine: treatment, 8.8 µmol/l; placebo, 8.1 µmol/l ***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 blood pressure between treatment and placebo groups: Heart rate, treatment: screening, 76.8; day 0, 74.0; day 14, 71.3 beats/min Heart rate, placebo: screening, 74.5; day 0, 73.2; day 14, 69.6 beats/min SBP, treatment: screening, 108.7; day 0, 108.9; day 14 = 106.5 mmHg SBP, placebo: screening, 111.3; day 0, 110.6; day 14, 105.3 mmHg DBP treatment: screening, 74.0; day 0, 69.7, day 14, 68.2 mmHg DBP, placebo: screening, 73.2; day 0, 71.4; day 14, 70.5 mmHg 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

continued

***TABLE 32* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (healthy subjects)*

Study details	Participant details	Results	Comments
Authors Lucini *et al*., 1998[57] ***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 criteria*** Inclusions: 27 volunteers from a smoking cessation programme ***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, 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 by 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 that '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**: –	–

continued

***TABLE 32* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (healthy subjects)*

Study details	Participant details	Results	Comments
Authors Sabha *et al.*, 2000[61] ***Study design*** RCT (crossover) ***Specific intervention*** Nicotine patch, 21 mg ***Comparator*** Placebo ***Duration of therapy*** Single dose study ***Duration of follow-up*** 1 day	***Number of participants*** Intervention: *n* = 21 Comparator: *n* = 21 ***Inclusion/exclusion criteria*** Inclusions: non-smokers or mild to moderate smokers ***Participant characteristics*** Sex: 12/21 male Mean ± SD age: non-smokers, 35.4 ± 4.2 years, smokers, 38.3 ± 7.1 years Mean ± SD years of tobacco use in smokers: 12.4 ± 5.2 Mean ± SD No. cigarettes/day: 12.2 ± 5.1 Mean ± SD Fagerstrom score: 3.5 ± 1.2 Mean ± SD expired CO: non-smokers, 3 ± 2 ppm; smokers, 9 ± 4 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: Mean ± SD percentage of maximum response to bradykinin: non-smokers, 54.3 ± 14.9; smokers, 48.3 ± 13.7 Mean ± SD percentage of maximum response to nitroprusside: non-smokers, 96 ± 25; smokers, 106 ± 42 Mean ± SD change in MABP: after 1 h in non-smokers from 87 ± 4 to 111 ± 5 mmHg; after 2 h in smokers from 83 ± 2 to 98 ± 6 mmHg Mean ± SD change in heart rate: only changed in non-smokers, from 69 ± 2 to 83 ± 3 beats/min at 1 h The increase in MABP and heart rate was accompanied by nausea, light-headedness, mild headache, and seating in non-smokers Thromboxane β_2 increased in non-smokers after 1 h use of patch **Clinical significance**: – **Comments**: the main finding 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) Mean ± SD percetage of maximum response to bradykinin: non-smokers, 88.1 ± 17.9; smokers, 56.0 ± 16.6 Mean ± SD percentage of maximum response to nitroprusside: non-smokers, 107 ± 23; smokers, 96 ± 25 There were no changes in MABP or heart rate in the placebo group **Comments**: –	–

continued

***TABLE 32* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (healthy subjects)*

Study details	Participant details	Results	Comments
Authors Krivokapich *et al.*, 1984[65] ***Study design*** RCT (crossover) ***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 h for each intervention or comparator ***Duration of follow-up*** NA (acute response study) **Note**: all participants abstained from cigarettes for a minimum of 11 h prior to study; treatments and comparators given randomly on consecutive days	***Number of participants*** Intervention: *n* = 6 Comparator: *n* = 6 ***Inclusion/exclusion criteria*** Inclusions: six paid volunteers with 'normal' resting blood pressure and 12-lead ECG at time of recruitment ***Baseline characteristics*** Sex: 100% male Mean ± SD age: 27.3 ± 2.6 years Mean ± SD No. cigarettes smoked per day: 26 ± 5 Mean ± SD No. years smoked: 8.8 ± 5.1 ***Proportion of participants reporting an adverse event*** Intervention: NA Comparator: NA	***Intervention*** **List of adverse events**: limited details reported; gum had no effect on CO; gum had no significant acute effect on heart rate; gum had no effect on blood pressure; gum had no acute effect on ECG **Comments**: no acute cardiovascular effects reported for nicotine gum ***Comparator*** **List of adverse events**: CO measured at 10 and 90 min from baseline: significant rise in CO ($p = 0.02$) at 10 min 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 SBP and DBP: increased in a dose-dependent manner at 5 min after cigarettes; gum had no effect Cigarettes increase CO acutely. Only the high nicotine cigarettes (2 mg) affect heart rate acutely. Cigarettes increase blood pressure acutely in a nicotine-dose-dependent manner. Cigarettes had no acute effect on the ECG **Comments**: NA	

DBP, diastolic blood pressure; ECG, electrocardiogram; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MABP, mean arterial blood pressure; NA, not applicable; SBP, systolic blood pressure

TABLE 33 *Adverse events with NRT reported in RCTs: cardiovascular events (participants with heart conditions)*

Study details	Participant details	Results	Comments
Authors Joseph *et al.*, 1996[55] ***Study design*** RCT ***Specific intervention*** Transdermal nicotine (Nicoderm) 21 mg/day for 6 weeks, 14 mg/day for 2 weeks and 7 mg/day for 2 weeks ***Comparator*** Placebo patch of same appearance and odour ***Duration of therapy*** 10 weeks ***Duration of follow-up*** 14 weeks (adverse event), 24 weeks (efficacy)	***Number of participants*** Intervention: *n* = 294 Comparator: *n* = 290 ***Inclusion/exclusion criteria*** Inclusions: minimum age 45 years; smoking minimum 15 cigarettes/day; must have smoked for at least 5 years, made a minimum of two previous attempts to quit and have an expired CO level of > 8 ppm; one or more of the following diagnosed conditions – history of myocardial infarction, history of coronary-artery bypass surgery or angioplasty, stenosis of at least 50% in at least one major coronary artery, as seen with coronary angiography, or a clinical history of angina, congestive heart failure, cor pulmonale, arrhythmia, peripheral vascular disease or cerebrovascular disease Exclusions: suffering from myocardial infarction, unstable angina, coronary-artery bypass graft, angioplasty or hospitalisation for cardiac arrhythmia in the 2 weeks before the study ***Baseline characteristics*** Mean age: treatment, 61 years; placebo, 60 years Mean No. cigarettes/day: treatment, 28; placebo, 28 Mean duration of smoking: treatment, 44 years; placebo, 44 years 2–5 previous attempts to quit: treatment, 184; placebo, 181 > 5 previous attempts to quit: treatment, 110; placebo, 109 Nicotine content of usual brand of cigarettes ≤ 0.9 mg: treatment, 140; placebo, 145 Mean Fagerstrom score: treatment, 6.4; placebo, 6.4 Mean expired CO: treatment, 25 ppm; placebo, 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; myocardial infarction, 0; cardiac arrest, 1; admission for increased severity of angina, 7; admission for arrhythmia, 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; out-patient visit for increased severity of athero-sclerotic 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; myocardial infarction, 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; out-patient visit for increased severity of athero-sclerotic cardiovascular disease, 7; total, 17 All end-points: 26 Not significantly different from control group **Comments**: NA ***Comparator*** **List of adverse events**: Primary end-points: death, 6; myocardial infarction, 1; cardiac arrest, 1; admission for increased severity of angina, 10; admission for arrhythmia, 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; myocardial infarction, 1; cardiac arrest, 0; admission for increased severity of angina, 5; admission for arrhythmia, 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**: NA **Comments**: NA	Patients in the treatment group gained an average of 1.4 kg between baseline and week 14 compared with 0.3 kg in the control group ($p = 0.001$). No significant differences in blood pressure or pulse

continued

***TABLE 33* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (participants with heart conditions)*

Study details	Participant details	Results	Comments
Authors Keeley *et al.*, 1996[62] ***Study design*** RCT ***Specific intervention*** In the sequence of cigarette (1 mg nicotine), 50 ml nicotine nasal spray (0.5 mg), second 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 h and all vasoactive medications (including β-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 criteria*** Inclusions: consecutive patients referred for cardiac catheterisation to evaluate chest pain who had smoked ≥ 10 cigarettes per day for ≥ 10 years Exclusions: > 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 male ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: see below **Comments**: NA ***Comparator*** **List of adverse events**: For the 45 non-diseased coronary arterial segments analysed (34 treatment group, 11 placebo group) there was a 5% (SD 2%) reduction in minimal luminal diameter ($p = 0.009$) compared with baseline after smoking first cigarette. The nine focally stenosed segments showed no significant reduction. Neither administration of nicotine spray nor smoking of the second cigarette caused a significant change in the minimum luminal diameter of either non-diseased or stenosed vessels Heart rate and systolic arterial pressure and, consequently, the rate–pressure product (estimate of myocardial oxygen demand) did not increase significantly except after smoking the first cigarette. Heart rate: baseline, 72 ± 3 beats/min, first smoke, 80 ± 3 beats/min ($p < 0.001$). Systolic arterial pressure: baseline, 136 ± 6 mmHg, first smoke, 142 ± 7 mmHg ($p = 0.0112$) **Comments**: cigarette smoking causes an acute increase in myocardial oxygen demand and concomitant coronary artery vasoconstriction. Subsequent increases in serum nicotine concentration (regardless of the method of delivery) have no further effect on these parameters. This may have consequences for decisions about NRT in patients who do not reliably discontinue smoking while on treatment	–

continued

***TABLE 33* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (participants with heart conditions)*

Study details	Participant details	Results	Comments
Authors Tzivoni *et al.*, 1996[66] ***Study design*** RCT ***Specific intervention*** Nicotine patches ***Comparator*** Placebo patches ***Duration of therapy*** 2 weeks ***Duration of follow-up*** 2 weeks **Note**: participants had 48 h of ambulatory ECG monitoring immediately before the study, for the first 48 h of patch application and after 2 weeks	***Number of participants*** Intervention: *n* = 52 Comparator: *n* = 54 ***Inclusion/exclusion criteria*** Inclusions: participants with coronary artery disease taking part in a smoking-cessation programme ***Baseline characteristics*** Not reported ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: no change in resting heart rate, SBP or DBP between screening and the two phases of the study. Number of ischaemic episodes: at screening, 2.5; after patch application 3.8; after 2 weeks, 2.9 (trend not significant). Duration of ischaemia: at screening, 22 min; after patch application, 25.7 min; after 2 weeks, 21.4 min (not significant) **Comments**: NA ***Comparator*** **List of adverse events**: no change in resting heart rate, SBP or DBP between screening and the two phases of the study. Number of ischaemic episodes: at screening, 3.5; after patch application, 5.0; after 2 weeks, 5.4 (trend not significant). Duration of ischaemia not stated **Comments**: NA	Conference abstracts; only limited information

continued

***TABLE 33* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (participants with heart conditions)*

Study details	Participant details	Results	Comments
Authors Tzivoni *et al.*, 1998[117] ***Study design*** RCT ***Specific intervention*** 14 or 21 mg/24 h (21 mg/24 h for smokers of ≥ 20 cigarettes/day) nicotine patches (Nicotinell) ***Comparator*** Placebo patches 2 and 3 mg/24 h ***Duration of therapy*** 2 weeks ***Duration of follow-up*** 2 weeks	***Number of participants*** Intervention: *n* = 52 Comparator: *n* = 54 ***Inclusion/exclusion criteria*** Inclusions: presence of coronary artery disease, based on angiography (> 70% narrowing of at least one major coronary artery), stable angina pectoris with positive exercise test, documented previous myocardial infarction; nicotine dependent, smoking at least 15 cigarettes/day for ≥ 5 years, with a Fagerstrom score of ≥ 5 Exclusions: hypersensitivity to any adhesive cutaneous application; myocardial infarction, coronary bypass surgery, coronary angioplasty or stroke within 3 months of screening; > 12 ischaemic episodes during 48 h ECG; DBP > 110 mmHg or SBP > 200 mmHg; reduced left ventricular function; clinical signs of congestive heart failure ***Baseline characteristics*** Sex: NRT patch, 48/52 male; placebo, 48/54 male Mean age: NRT patch, 54.5 years; placebo, 53.1 years Mean smoking duration: NRT patch, 36 years; placebo, 35 years Mean No. cigarettes/day: NRT patch, 25; placebo, 28 Mean Fagerstrom score: NRT patch, 7.7; placebo, 7.8 Mean No. of previous attempts to stop smoking: NRT patch, 2.1; placebo, 1.6 Mean nicotine content per cigarette: NRT patch, 0.9; placebo, 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 one patient developed unstable angina with documented ischaemia. Heart rate, blood pressure, ambulatory ECG and exercise testing showed no significant differences between treatment and control groups during the study **Comments**: NA ***Comparator*** **List of adverse events**: one patient who had worsening angina underwent cardiac catheterisation and coronary artery bypass surgery **Comments**: NA	Efficacy: treatment group, 14 (52%) claimed abstinence at 2 weeks; control group, 7 (13%) claimed abstinence at 2 weeks. 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

continued

***TABLE 33* contd** *Adverse events with NRT reported in RCTs: cardiovascular events (participants with heart conditions)*

Study details	Participant details	Results	Comments
Authors Working Group for the Study of Transdermal Nicotine in Patients with CAD, 1994[55] ***Study design*** RCT ***Specific intervention*** Nicotine patch 14–21 mg/day ***Comparator*** Placebo ***Duration of therapy*** 5 weeks ***Duration of follow-up*** 5 weeks	***Number of participants*** Intervention: *n* = 77 Comparator: *n* = 79 ***Inclusion/exclusion criteria*** Inclusions: smokers with stable coronary artery disease ***Participant characteristics*** Mean ± SD age: patch, 56.0 ± 7.5 years; placebo, 55.9 ± 8.1 years Sex: 124/156 male Mean No. of cigarettes/day: 33 Mean No. years smoked: 38 Mean Fagerstrom score: 8 Average No. 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 2.2 kg (greater than placebo, $p < 0.05$). Weight gain was greater in those who stopped smoking: mean 3.3 kg ($p < 0.05$ compared with placebo). Adverse events were reported by 50% of patients in each treatment group; however, only transient itching at the patch application site was reported more often on active treatment than placebo (36% vs 9%). Mean changes in blood chemistry and haematology variables were generally not significantly different between active and placebo treatments **Comments**: NA ***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 1.3 kg and was greater in those who stopped smoking: mean 3.3 kg. Adverse events reported more often on placebo than on active treatment were dizziness, insomnia, diarrhoea, body aches, nervousness and angina **Comments:** NA	Short-term use of nicotine patch: only 5 weeks

TABLE 34 *Adverse events with NRT reported in RCTs: pregnancy*

Study details	Participant details	Results	Comments
Authors Hardardottir *et al.*, 1996[118] (main publication of this study is Oncken *et al.*, 1997[71]) ***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: *n* = 13 Comparator: unclear ***Inclusion/exclusion criteria*** Inclusions: pregnant females, aged ≥ 18 years, 24–36 weeks gestation, who smoked at least 15 cigarettes/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 ($p < 0.01$; $n = 7$). Maternal heart rate, fetal heart rate and RI in uterine artery, umbilical artery and middle cerebral artery 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 blood pressure with patch compared with smoking with comparable nicotine blood levels may suggest some adverse effect of patch. No difference in fetal cardiovascular effects **Comments**: NA ***Comparator*** **List of adverse events**: see above **Comments**: NA	Same study as full manuscript: Oncken *et al.*, 1997[71]

continued

***TABLE 34* contd** *Adverse events with NRT reported in RCTs: pregnancy*

Study details	Participant details	Results	Comments
Authors Oncken *et al.*, 1997[71] (also published as Hardardottir *et al.*, 1996[120]) ***Study design*** RCT (crossover) ***Specific intervention*** 21 mg nicotine patch ***Comparator*** Smoking *ad libitum* ***Duration of therapy*** 8 h ***Duration of follow-up*** Concurrent with study	***Number of participants*** Intervention: *n* = 15 Comparator: *n* = 15 ***Inclusion/exclusion criteria*** Inclusions: ≥ 18 years old, gestation 24–36 weeks, self-reported smoking of 15 cigarettes/day for preceding year Exclusions: fetal growth restriction (estimated fetal weight < 10th centile for gestational age), hypertension (blood pressure ≥ 14/90 mmHg), alcohol or illegal drug use during this pregnancy, positive urine toxicology screen, use of other tobacco products, salivary cotinine ≤ 85 ng/ml, fetal anomalies, fetal 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 weeks 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-h/ml ($p = 0.77$ compared to whilst smoking). The mean ± SD change in the middle cerebral artery RI from baseline to 4 h later was –0.0002 ± 0.008 ($p = 0.3$ compared to whilst smoking). No clinically significant adverse event or pregnancy complications during study. Significant time effects for SBP ($p < 0.001$) and maternal heart rate ($p < 0.001$) occurred 2 h after baseline measurements. DBP changed significantly over time ($p = 0.007$) and the condition–time interaction was significant ($p = 0.004$) **Comments**: changes in the middle cerebral RI are an indirect measure of fetal hypoxia. Acute effects of nicotine on measures of fetal well-being are apparently similar regardless of method of delivery ***Comparator*** **List of adverse events**: the plasma AUC for nicotine during patch use was 89 ng-h/ml ($p = 0.77$ compared to whilst using patch). The mean ± SD change in the middle cerebral artery RI from baseline to 4 h later was –0.02 ± 0.015 ($p = 0.3$ compared to using patch) **Comments**: NA	The study had > 80% power to detect a 25% difference an a change of 2 SDs in the middle cerebral artery RI between treatments. The study was primarily designed to compare acute effects of smoking and nicotine patch; short-term use only, with no follow-up monitoring of adverse events

continued

***TABLE 34* contd** *Adverse events with NRT reported in RCTs: pregnancy*

Study details	Participant details	Results	Comments
Authors Wisborg *et al.*, 2000[31] ***Study design*** RCT ***Specific intervention*** Nicotine patch (16 h), 15 mg (8 weeks), 10 mg (3 weeks) ***Comparator*** Placebo ***Duration of therapy*** 11 weeks ***Duration of follow-up*** During pregnancy and up to 12 months post-partum	***Number of participants*** *n* = 124 ***Inclusion/exclusion criteria*** Inclusions: healthy pregnant women who smoked ≥ 10 cigarettes/day and were < 22 weeks pregnant ***Baseline characteristics*** Mean age: 28 years Mean ± SD consumption of cigarettes/day: nicotine, 13.4 ± 4.0; placebo, 14.2 ± 4.4 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 3457 g in the nicotine group and 3271 g in the placebo group (mean difference 186 g (95% CI, 35 to 336). Proportion of infants with weight < 2500 g 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 3539 g and 3381 g, respectively (mean difference 157 g; 95% CI, 25 to 291). The rate of preterm delivery was 8% in the nicotine group and 10% in the placebo group (RR = 0.8; 95% CI, 0.4 to 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 the data cannot reliably inform about the safety or otherwise of using nicotine patches in pregnancy	–

MCA, Medicines Control Agency; RI, resistance index

TABLE 35 *Adverse events with NRT reported in RCTs: diabetes mellitus*

Study details	Participant details	Results	Comments
Authors Epifano *et al.*, 1992[63] ***Study design*** RCT (crossover) ***Specific intervention*** Nicotine patch (30 cm^2) ***Comparator*** Placebo; smoking ***Duration of therapy*** 2 days ***Duration of follow-up*** After 12 h	***Number of participants*** Intervention: *n* = 12 Comparator: *n* = 12, in each group ***Inclusion/exclusion criteria*** Inclusions: patients with a Fagerstrom score of 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**: mean ± SEM baseline plasma glucose: after nicotine patch, 8.5 ± 0.29 mmol/l; after placebo, 8.7 ± 0.33 mmol/l; after smoking, 8.6 ± 0.26 mmol/l (differences not significant). 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 (mean ± SEM: 11.2 ± 0.31, 10.6 ± 0.30 and 10.4 ± 0.34 μmol/kg/min) **Comments**: 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 that action of insulin, but does so to a lesser extent than seen with cigarette smoking ***Comparator*** **List of adverse events**: see above **Comments**: NA	Crossover study – patch, placebo or smoking Nicotine patch may represent a 'metabolically' safe measure to help participants with type 2 diabetes give up smoking

SEM, standard error of the mean

TABLE 36 *Adverse events with NRT reported in RCTs: abuse potential*

Study details	Participant details	Results	Comments
Authors Hurt *et al.*, 1995[67] ***Study design*** RCT ***Specific intervention*** Nicotine gum ***Comparator*** NA ***Duration of therapy*** Cessation ***Duration of follow-up*** 6 weeks	***Number of participants*** *n* = 26, divided between tapering regimens ***Inclusion/exclusion criteria*** Inclusions: 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 pieces/day) for a median of 36 months (range 14–56 months) 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 6 weeks the proportion of participants who had not relapsed to gum or smoking were 67% (95% CI, 29.9 to 92.5) for the abrupt withdrawal group, 71.4% (95% CI, 29.1 to 96.3) for the taper with placebo gum group, and 60% (95% CI, 26.2 to 87.8) for the taper with active gum group **Comments**: NA	Small sample size and short duration of follow-up limit reliability of findings
Authors West *et al.*, 2000[70] ***Study design*** RCT ***Specific intervention*** Nicorette gum, 2 or 4 mg; Nicorette transdermal 16 h patch, 15 mg; Nicorette nasal spray; Nicorette inhaler ***Comparator*** None ***Duration of therapy*** Up to 14 weeks ***Duration of follow-up*** 15 weeks	***Number of participants*** Gum, *n* = 127 Transdermal patch, *n* = 124 Nasal spray, *n* = 126 Inhaler, *n* = 127 Total, *n* = 504 ***Inclusion/exclusion criteria*** Inclusions: aged ≥ 18 years, smoked ≥ 10 cigarettes/day; motivated to give up smoking; good general health; 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: Mean ± SD amount of product used since last visit, week 15: gum, 2.5 ± 2.6; patch, 0.3 ± 0.2; spray, 4.8 ± 4.0; inhaler, 1.0 ± 1.3 Mean ± SD pleasantness/unpleasantness (and satisfaction) compared with cigarettes, week 4: gum, 5 ± 3.2; patch, 6.5 ± 3.8; spray, 4.6 ± 4.0; inhaler, 5.2 ± 4.0 How dependent they were on their product, week 15: gum, 22%; patch, 0%; spray, 20%; inhaler, 33% Proportion of participants still using NRT at week 15: gum, 7%; patch, 2%; spray, 10%; inhaler, 7% **Comments**: NA	

TABLE 37 *Adverse events of NRT reported in RCTs: cutaneous reactions*

Study details	Participant details	Results	Comments
Authors Jordan, 1992[68] ***Study design*** RCT ***Specific intervention*** Nicotine patch (2.5 cm^2, 12.5 mg nicotine, 3.8 mg/24 h, each patch for 48 h) ***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 criteria*** Inclusions: healthy men and women smokers, aged 18–65 years Exclusions: pregnant or lactating women; significant medical condition; significant dermatological 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 female Mean ± SD age: 38.2 ± 11.1 years (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 proportion with no reaction to the patches ranged from 8.6% to 58.1%. The proportion 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 **List of adverse events, phase 2**: contact sensitisation occurred in three cases with the active patch, but in 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 and 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**: the study indicates that transdermal nicotine has a low potential for contact sensitisation and skin irritation	Small sample size and short duration of follow-up limit reliability of findings. Study used 48 h patches, not the 16 or 24 h application used with commercially available patches. Skin reactions were possibly greater in this study than with shorter duration patches

TABLE 38 *Adverse events with NRT reported in RCTs: body weight*

Study details	Participant details	Results	Comments
Authors Nordstrom *et al.*, 1999[69] ***Study design*** RCT ***Specific intervention*** Nicotine gum, 2 or 4 mg, 9–15 pieces/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 criteria*** Inclusions: 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 year. Participants were at least 20 years old and in good health ***Participant characteristics*** Age range: 43–45 years No. cigarettes smoked per day: 21.5–24.3; no difference between those in the placebo, 2 mg gum and 4 mg gum groups Groups comparable for age, gender, race and smoking habits ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: BMI (mean ± SD): 2 mg gum – baseline 25.3 ± 4.3, change after 1 year 1.2 kg/m^2; 4 mg gum – baseline 28.2 ± 6.2, change after 1 year 1.3 kg/m^2 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 1 year the difference has been eroded **Comments**: NA ***Comparator*** **List of adverse events:** BMI (mean ± SD): baseline 26.7 ± 5.7, change after 1 year 1.2 kg/m^2 **Comments**: NA	This paper is a follow-up of Doherty *et al.*, 1996,[519] in which the same group of participants had been followed for only 3 months

BMI, body mass index

TABLE 39 *Adverse events of NRT reported in RCTs: endothelial function*

Study details	Participant details	Results	Comments
Authors Neunteufl *et al.*, 2001[58] ***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 min ***Duration of follow-up*** Concurrent with study	***Number of participants*** Intervention: unclear Comparator: unclear ***Inclusion/exclusion criteria*** Inclusions: total of 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 (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**: –	–

ANOVA, analysis of variance

TABLE 40 *Adverse events with NRT reported in non-RCTs: cardiovascular events*

Study details	Participant details	Results	Comments
Authors Benowitz *et al.*, 1993[74] ***Study design*** Non-RCT (crossover) ***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 criteria*** Inclusions: 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**: a 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-dehydrothromboxane B_2 and increased plasma concentrations of the platelet α-granule constituents platelet factor IV and β-thromboglobulin, indicating *in vivo* platelet activation. These effects were statistically significantly different from those seen with the placebo patch **Comments**: NA	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 treatment of patients with ischaemic heart disease is likely to be safer than smoking"
Authors Netscher *et al.*, 1995[72] ***Study design*** Non-randomised, controlled, crossover study ***Specific intervention*** Nicotine patch (PROSTEP 22 mg/day, 24 h) ***Comparator*** Two cigarettes, or 48 h no smoking ***Duration of therapy*** 34 h ***Duration of follow-up*** Duration of testing	***Number of participants*** Intervention: *n* = 30 Comparator: *n* = 30 ***Inclusion/exclusion criteria*** Inclusions: healthy volunteers who were habitual smokers ***Baseline characteristics*** Mean age: 48 years (range 36–72 years) Sex: 25/30 male ***Proportion of participants reporting an adverse event*** Intervention: NA Comparator: NA	***Intervention*** **List of adverse events**: no significant effect on oxygen saturation, carboxyhaemoglobin and catecholamine concentrations, plasma osmolality, vasopressin or fibrinogen concentrations, haematocrit, or white cell or platelet counts, compared with control of 48 h smoking abstinence. 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. Blood pressure 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**: – ***Comparator*** **List of adverse events**: relative blood flow when smoking was significantly decreased compared with non-smoking control. Average heart rate, blood pressure, 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**: –	–

continued

***TABLE 40* contd** *Adverse events with NRT reported in non-RCTs: cardiovascular events*

Study details	Participant details	Results	Comments
Authors Zevin *et al.*, 1998[73] ***Study design*** Non-RCT ***Specific intervention*** 0, 21, 42 and 63 mg/24 h transdermal nicotine ***Comparator*** None ***Duration of therapy*** 21 days; 5 for each (smoking during first 4 days) ***Duration of follow-up*** Concurrent with study	***Number of participants*** *n* = 12 ***Inclusion/exclusion criteria*** Inclusions: healthy male smokers with no interest in stopping smoking, who smoked at least 20 cigarettes/day and whose plasma cotinine levels were at least 150 ng/ml Exclusions: chronic illness, medication use, drug abuse or use of alcohol > 30 g/day Study conducted in hospital ***Baseline characteristics*** Mean ± SD age: 41 ± 6 years Mean ± SD No. cigarettes/day: 29 ± 9 Mean ± SD plasma cotinine level: 340 ± 88 ng/ml ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **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 h did not differ across the treatments. Effects unlikely to be of any significance given the small sample size and difficulty involved in accurate 24 h urine measurements **Comments**: –	Heart rate, SBP and DBP over 24 h 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 haematocrit, white blood cell count, fibrinogen level or lipid profile across the different patch doses. High-dose nicotine treatment, even with concomitant smoking, caused no acute adverse cardiovascular effects

TABLE 41 *Adverse events with NRT reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Fredrickson *et al.*, 1995[75] ***Study design*** Uncontrolled study ***Specific intervention*** Transdermal nicotine patch (4 weeks, 44 mg/day) ***Comparator*** None ***Duration of therapy*** 4 weeks ***Duration of follow-up*** 4 weeks	***Number of participants*** *n* = 40 ***Inclusion/exclusion criteria*** Inclusions: heavy smokers ***Baseline characteristics*** Mean ± SD age: 32.4 ± 9.8 years Sex: 20/40 male Mean smoking rate: 32.4 cigarettes/day Mean No. years smoking: 28.8 Mean Fagerstrom score: 7.3 15% had previously tried to stop smoking at least five times ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: mention of skin reactions, but the dose period in which they occurred was not specified (erythema only, 52.5%; erythema with oedema, 15.0%; erythema with vesicales, 5.0%; bullae/ erosions, 2.5%; itching only, 7.5%). Mention other minor adverse events (mild, self-limiting cardiovascular symptoms – tight chest, racing heart, light-headedness; nausea; vomiting; headache), but do not give absolute numbers or percentages 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 adverse events **Comments**: none	Authors do not report absolute numbers or percentages of participants suffering from the adverse events in a number of cases. An uncontrolled study where all participants were given 44 mg/day patches for 4 weeks, immediately followed by 22 mg/day patches for 4 weeks. Data are poorly presented

continued

***TABLE 41* contd** *Adverse events with NRT reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Gourlay *et al.*, 1999[76] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine patch, 21 mg (24 h), reducing to 14 mg after 4 weeks, 7 mg at 8 weeks and none after 12 weeks (also included brief counselling and a booklet) ***Comparator*** None ***Duration of therapy*** Unclear ***Duration of follow-up*** Unclear	***Number of participants*** *n* = 1481 (follow-up on 1392) ***Inclusion/exclusion criteria*** Inclusions: age 18–70 years; strong desire to quit smoking had smoked at least 15 cigarettes/day for the previous 3 years Exclusions: those taking medication that might interfere with nicotine withdrawal symptoms ***Participant characteristics*** Mean ± SD age: 41 ± 11 years Sex: 56% female Mean ± SD No. cigarettes/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	***Intervention*** **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, were born outside Australasia, or had a university or trade school education, but these associations were modest (adjusted hazard ratios 0.8–1.8). There was no association between pre-existing skin disorders and moderate to 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 4–14 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/light-headedness	**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 to be little additional risk of moderate to severe application site reactions in participants with a history of skin disorders

continued

***TABLE 41* contd** *Adverse events with NRT reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Hurt *et al.*, 1998[77] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine nasal spray, 1–2 mg/h ***Comparator*** None ***Duration of therapy*** 7 days ***Duration of follow-up*** 7 days	***Number of participants*** *n* = 50 ***Inclusion/exclusion criteria*** Inclusions: smokers ***Baseline characteristics*** Sex: 27/50 male Mean (SD) age: 43.7 (11.5) years Mean ± SD No. cigarettes/day: 28.5 ± 11.3 (range 15–65) Mean ± SD No. 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	***Intervention*** **List of adverse events**: Scores reported for specified symptoms (baseline and mean for days 1–7): runny nose 0.1 and 1.3; nasal irritation 0.1 and 1.2; throat irritation 0.2 and 1.0; watering eyes 0.1 and 0.9; sneezing 0.2 and 0.8; alertness 1.6 and 1.2; calmness 1.6 and 1.1; high feeling 0.8 and 0.7; coughing 0.8 and 0.6; sweating 0.8 and 0.5; headache 0.4 and 0.4; light-headedness < 0.1 and 0.2; nausea < 0.1 and 0.1; dizziness < 0.1 and 0.1; pounding heart 0.1 and < 0.1; cold hands and feet < 0.1 and < 0.1 Symptoms reported by 10% or more of participants were headache. 17; burning sensation of nose, throat or unspecified areas, 14; watering eyes, 13; nasal irritation, 12; throat irritation, 12; sneezing, 9; runny nose, 9; cough, 7; awakening during the night or early awakening, 5. One patient (72-year-old female) suffered a stroke. One patient experienced exacerbation of old emotional problems and one participant experienced abdominal pain and subsequently underwent cholecystectomy. The last two events were not considered to be related to the use of the spray **Comments**: the most frequent adverse experiences were headache, burning sensation, watering eyes, nasal and throat irritation and sneezing	–

continued

***TABLE 41* contd** *Adverse events with NRT reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors House *et al.*, 1995[80] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine patch, 22 mg tapering to 11 mg ***Comparator*** None ***Duration of therapy*** 8 weeks ***Duration of follow-up*** 6 months	***Number of participants*** *n* = 22 ***Inclusion/exclusion criteria*** Inclusions: adolescent smokers ***Baseline characteristics*** Sex: 68% female Mean ± SD age: 15.9 ± 1.3 years Mean ± SD No. cigarettes/day: 23.3 ± 5 Mean ± SD years smoking: 2.6 ± 1.6 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **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, or led to the discontinuation of patch therapy **Comments**: nicotine patch is apparently safe and well tolerated in adolescents	–
Authors Bende *et al.*, 1998[78] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine nasal spray, 0.5 mg/shot (1 mg/dose) **Note**: dosage of nasal spray was 1 dose/h for the first week, then *ad libitum* thereafter, with gradual reduction encouraged. 79% still used the spray at the visit in week 20 ***Comparator*** None ***Duration of therapy*** Up to 20 weeks ***Duration of follow-up*** 20 weeks	***Number of participants*** *n* = 40 ***Inclusion/exclusion criteria*** Inclusions: age > 18 years, with a well-documented history of chronic rhinitis and/or chronic sinusitis and had smoked at least 15 cigarettes/day for more than 3 years ***Baseline characteristics*** Mean age: 45 years (range 26–71 years) Sex: 17/40 male Mean ± SD No. cigarettes/day: 22 ± 6 Mean ± SD No. years smoked: 28 ± 10 ***Proportion of participants reporting an adverse event*** Not reported	***Intervention*** **List of adverse events**: Incidence (%) 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 (not significant) Nasal cytology: 19/29 evaluable participants showed an improvement; 5/29 showed no change; 5/29 showed a deterioration	**Comments**: 38% of participants were abstainers at week 12 and 35% at week 20. Numbers were not reported in paper, so attrition and dropouts due to adverse events is not known

continued

***TABLE 41* contd** *Adverse events with NRT reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Bjornson-Benson *et al.*, 1993[79] ***Study design*** Uncontrolled study **Note**: population consisted of participants from an RCT: only those previously randomised to NRT and who had continued to use NRT for 1 year were included in this uncontrolled study ***Specific intervention*** Nicotine gum, 2 mg ***Comparator*** None ***Duration of therapy*** Up to 12 months ***Duration of follow-up*** 12 months	***Number of participants*** *n* = 3923 ***Inclusion/exclusion criteria*** Inclusions: participants were those who entered the Lung Health Study and were randomised to a special intervention rather than usual care. All participants in the study were aged 35–60 years, with mild to moderate airflow obstruction (FEV/FVC ≤ 7) Exclusions: patients with a lung condition that affected lung function or if they were unlikely to participate in the 5-year follow-up ***Participant characteristics*** Sex: 63% male Mean age: 48 years Average No. of cigarettes/day: 31 ***Proportion of participants reporting an adverse event*** Not reported	***Intervention*** **List of adverse events**: mouth irritation, 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 was given on the adverse events reported by gum users who did not achieve abstinence **Comments**: NA	–

TABLE 42 *Adverse events of NRT reported in uncontrolled studies: cardiovascular events (healthy subjects)*

Study details	Participant details	Results	Comments
Authors Sarabi *et al.*, 2000[86] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine gum (Nicorette, 4 mg) ***Comparator*** Smoking one cigarette (0.9 mg nicotine) over 4–5 min; no real comparison made between treatments ***Duration of therapy*** 30 min ***Duration of follow-up*** 30 min	***Number of participants*** Intervention: *n* = 16 Comparator: *n* = 16 ***Inclusion/exclusion criteria*** Inclusions: young (20–25 years), healthy, regular smokers; not taking any regular medication; no history of any disease known to affect the cardiovascular system, or any metabolic or other serious disease ***Baseline characteristics*** Sex: 7/16 male Smoked > 10 cigarettes/day: 4/16 Smoked 5–10 cigarettes/day: 6/16 Smoked < 5 cigarettes/day: 6/19 Mean ± SD duration of smoking: 5 ± 3 years All participants had fasted overnight and abstained from smoking for at least 8 h before the study. Measurements were made with the participants in a supine position in an air-conditioned room at a constant temperature of 20°C ***Proportion of participants reporting an adverse event*** Intervention: not reported; specific short-term effects only Comparator: not reported; specific short-term effects only	***Intervention*** **List of adverse events**: nicotine gum increased MAP, heart rate and cardiac index significantly ($p < 0.05$ for all), but not resting FBF, resting FVR or 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; $p < 0.05$ for plateau phase) **Clinical significance**: *p* values given above **Comments**: NA ***Comparator*** **List of adverse events**: MAP, cardiac index and resting FBF changed significantly during smoking. An increase was seen in all 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 the early and the plateau phases ($p < 0.01$ and $p < 0.05$, respectively). Resting FVR and TPRI remained unchanged during both the early and the plateau phases. The index of endothelial function (ratio of FVR with vasodilatory drug given in the 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	–

continued

***TABLE 42* contd** *Adverse events of NRT reported in uncontrolled studies: cardiovascular events (healthy subjects)*

Study details	Participant details	Results	Comments
Authors Stein *et al*., 1996[87] ***Study design*** Uncontrolled study ***Specific intervention*** Transdermal nicotine patches (Nicoderm; 21, 14 and 7 mg) ***Comparator*** Smoking (baseline); quitting smoking ***Duration of therapy*** 10 weeks (21 mg for 6 weeks; 14 mg for 2 weeks; 7 mg for 2 weeks) ***Duration of follow-up*** 14 weeks (4 weeks following cessation of patch use)	***Number of participants*** Intervention: *n* = 54 Comparator: own controls ***Inclusion/exclusion criteria*** Inclusions: 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 Exclusions: 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 male Mean ± SD age: 43 ± 12 years ***Proportion of participants reporting an adverse event*** Intervention: NA Comparator: NA	***Intervention*** **List of adverse events**: ECG recordings from those participants who achieved total abstinence throughout the study demonstrated that heart rate decreased and heart-rate variability increased as participants switched from smoking to patch and again from patch to smoking. Note: heart-rate variability is a non-invasive measure of autonomic tone Use of the 21 mg transdermal nicotine patch reduced heart rate and increased heart-rate variability **Comments**: NA ***Comparator*** **List of adverse events**: see above Mean ± SD breath frequency: 0.266 ± 0.040 Hz; 0.248 ± 0.033 Hz (p = 0.009 compared to baseline) **Comments**: NA	20/54 participants provided recordings after completing 10 weeks of treatment. 4/54 participants discontinued use of the patch before the second recording; a final smoke-free recording was obtained 4 weeks after discontinuation of the 21 mg patch

FBF, forearm blood flow; FVR, forearm vascular resistance; MAP, mean arterial pressure; TPRI, total peripheral resistance index

TABLE 43 *Adverse events of NRT reported in uncontrolled studies: cardiovascular events (participants with heart conditions)*

Study details	Participant details	Results	Comments
Authors Mahmarian *et al.*, 1997[88] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine patches (Nicoderm, 14 and 21 mg) ***Comparator*** None ***Duration of therapy*** Minimum 6 days ***Duration of follow-up*** None (acute study)	***Number of participants*** *n* = 40 ***Inclusion/exclusion criteria*** Inclusions: coronary artery disease on angiography; smoked at least 1 pack of cigarettes per day, but had a strong desire to quit; and had a qualifying abnormal SPECT (at least 5% exercise-induced reversible perfusion defect) Exclusions: unstable angina, recent (< 3 months) coronary angioplasty or bypass surgery, significant valvular heart disease or intolerance to nicotine preparations ***Baseline characteristics*** Sex: 32/40 male Mean ± SD age: 55 ± 10 years Mean ± SD No. years smoked: 40 ± 12 Mean ± SD No. cigarettes smoked/day: 31 ± 11 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: patients had no significant change in any of their treadmill exercise haemodynamic variables (heart rate, SBP, DBP and rate–pressure product) from baseline to 14 mg and 21 mg patch therapy. In the 14 participants who had demonstrated exercise-induced ST-elevation, the time to 1 mm 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 ($p < 0.001$) was observed from baseline (mean ± SD, 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 an at least 9% decrease in their total perfusion defect size from baseline to 14 mg patch therapy, and 10/34 participants from baseline to 21 mg patch therapy. No patient had an at least 9% increase in perfusion defect size 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**: the authors state "Because cardiac risk is known to be directly related to the extent of exercise-induced perfusion defect size, 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**: NA	Study did not have the power to detect potential adverse clinical events associated with nicotine patch therapy

continued

***TABLE 43* contd** *Adverse events of NRT reported in uncontrolled studies: cardiovascular events (participants with heart conditions)*

Study details	Participant details	Results	Comments
Authors Nitenberg and Antony, 1999[89] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine gum (Nicorette, 4 mg) ***Comparator*** NA ***Duration of therapy*** Single dose ***Duration of follow-up*** Acute	***Number of participants*** *n* = 17 ***Inclusion/exclusion criteria*** Inclusions: 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 1 year); all drugs that may alter coronary vasomotion (beta-blocking agents, calcium antagonists, long-acting nitrates, molsidomine, angiotensin-converting enzyme inhibitors) were discontinued 7 days before the investigation Exclusions: history suggestive of unstable angina or myocardial infarction; congestive heart failure; chest pain during the coronary arteriography ***Baseline characteristics*** Sex: 12/17 male Mean ± SD age: 55 ± 10 years ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: cold pressure test produced similar increases in arterial presure from baseline, without a change in heart rate, before and after nicotine gum. Nicotine gum does not appear 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 is not a risk for precipitating coronary artery constriction, and therefore this is not a reason not to use it in participants with coronary artery disease	Small study measuring acute effects only, in ex-smokers

SPECT, single photon emission computed tomography

TABLE 44 *Adverse events of NRT reported in uncontrolled studies: pregnancy*

Study details	Participant details	Results	Comments
Authors Ogburn *et al.*, 1999[92] ***Study design*** Uncontrolled study ***Specific intervention*** 22 mg/24 h nicotine patch ***Comparator*** NA ***Duration of therapy*** 4 days ***Duration of follow-up*** Concurrent with study	***Number of participants*** *n* = 21 ***Inclusion/exclusion criteria*** Inclusions: cigarette smokers, smoking ≥ 15 cigarettes/day; third trimester of pregnancy; age ≥ 18 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 Exclusions: recent history (preceding 6 months) 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 weeks Mean ± SD current No. cigarettes/day: 20.5 ± 8.7 Mean ± SD No. smoking years: 11.0 ± 6.1 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: during the 4 days of smoking abstinence and nicotine patch use morning fetal heart rates were significantly reduced relative to baseline when smoking *ad libitum* was permitted Mean ± SD baseline fetal heart rate: morning, 142 ± 7.6; afternoon 141.4 ± 7.0 Mean ± SD day 4 fetal heart rate: morning, 135.8 ± 7.3 (p = 0.017 vs baseline); afternoon, 143 ± 11.9 (NS vs baseline) Mean ± SD baseline SBP/DBP ratio: morning, 3.7 ± 1.0; afternoon, 3.4 ± 0.7 Mean ± SD day 4 SBP/DBP ratio: morning, 3.5 ± 0.7; afternoon, 3.6 ± 1.2 (NS vs baseline) Baseline, non-reactive: morning, 4.6%; afternoon, 4.8% Day 4, non-reactive: morning, 5.0% (NS vs baseline); afternoon, 0.0% **Comments**: no evidence of acute fetal compromise during NRT	Study designed to assess only acute fetal and maternal effects of NRT

continued

***TABLE 44* contd** *Adverse events of NRT reported in uncontrolled studies: pregnancy*

Study details	Participant details	Results	Comments
Authors Wright *et al.*, 1997[93] ***Study design*** Uncontrolled study ***Specific intervention*** Single dose, 21 mg nicotine patch ***Comparator*** None ***Duration of therapy*** 8 h ***Duration of follow-up*** 8 h **Note**: study conducted as inpatients over 21 h during which patients abstained from smoking	***Number of participants*** *n* = 6 ***Inclusion/exclusion criteria*** Inclusions: 27–38 weeks gestation; recalcitrant to 'standard care' for smoking cessation; 'low risk', no obstetric or medical problems and taking no medication except vitamin or iron supplements; singleton pregnancy, normal by ultrasonographic scan; negative screen for substance abuse; age < 35 years; smoking minimum of half pack/day ***Baseline characteristics*** Mean maternal age: 25.7 years (range 21–31 years) Mean weight: 82.05 kg (range 66.1–87.5 kg) (one outlier at 100.7 kg) Mean gestational age: 34.2 weeks (range 28.1–37.0 weeks) Mean estimated fetal weight: 2288 g (range 1185–2736 g) Smoked 0.5–2 pack/day ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: no measurable differences in fetal 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 fetal heart rate decelerations or baseline changes and umbilical artery Doppler readings were unchanged. No fetus had clinically significant changes in minute variation, accelerations or baseline fetal 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

TABLE 45 *Adverse events of NRT reported in uncontrolled studies: cutaneous reaction*

Study details	Participant details	Results	Comments
Authors Bircher *et al.*, 1991[84] ***Study design*** Uncontrolled study ***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 criteria*** Inclusions: volunteers who had experienced cutaneous side-effects from the use of the nicotine patch ***Baseline characteristics*** Sex: 10/14 male 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	***Intervention*** **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, 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. One ex-smoker experienced acute tachycardia and sweating after application of 30 mg nicotine base **Clinical significance**: – **Comments**: three types of reaction were identified: irritation due to accumulation of humidity, sweat or bacterial growth under patch (not of great importance due to short term (≤ 24) exposure to each patch); contact urticarial reaction due to local effect of nicotine on the cutaneous vasculature; and contact sensitisation to a component of the patch or an active ingredient	–
Author Mills *et al.*, 1997[85] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine patch (16 h, 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 criteria*** Inclusions: life-long smokers Exclusions: 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 male Mean age: 35.4 years (range 24–44 years) ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: significant reduction in cutaneous inflammatory 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 weeks. There was no change in blood flow following application of topical nicotinates **Comments**: nicotine delivered by patch transiently suppresses cutaneous inflammatory response	–

TABLE 46 *Adverse events of NRT reported in uncontrolled studies: oral mucosa*

Study details	Participant details	Results	Comments
Authors Wallstrom *et al.*, 1999[83] ***Study design*** Uncontrolled study ***Specific intervention*** Sublingual nicotine tablet (2 mg nicotine) ***Comparator*** NA ***Duration of therapy*** Up to 6 months ***Duration of follow-up*** 12 months	***Number of participants*** *n* = 30 ***Inclusion/exclusion criteria*** Inclusions: healthy volunteers who were smoking at least 10 cigarettes/day Exclusions: pregnant or breast-feeding women; individuals with pre-existing mouth lesions, acute medical illnesses, history of severe or symptomatic cardiovascular disease, taking regular psychotropic medication or history of alcohol/drug abuse ***Baseline characteristics*** Sex: 12/30 male Mean age: men, 45.2 years (range 29.3–62.4 years); women, 39.4 years (range 25.8–50.6 years) Fagerstrom score > 7: 23/30 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: lesions on floor of mouth, *n* = 8 participants (all occurred during weeks 1–6 and healed by 6 months). Of those lesions biopsied (*n* = 11), one consisted of keratinised mucosa, one of hyperplastic mucosa and in four inflammatory cells were present. Lesions at other sites in the mouth: *n* = 15 at baseline; *n* = 6 at 12 months Other adverse events: the most frequent self-reported adverse events were hiccups (*n* = 13), a burning/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**: NA	Low-nicotine-dependent participants were told to use 1 tablet/h up to a maximum of 20 tablets/day; and high-nicotine-dependent participants were told to use 2 tablets/h up to a maximum of 40 tablets/day. During the first week of treatment the daily dose ranged from 7 to 38 tablets/day (mean 23) in subjects with a Fagerstrom score of ≥ 7, and from 3 to 17 tablets/day in those with a score of < 7. Compliance at 6 weeks was high, with 90% of participants using at least 1 tablet/day (mean 23 tablets/day). Mean overall tablet consumption at 6 months was 7 (low-dependency) and 12 (high-dependency) tablets/day. The different 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

TABLE 47 *Adverse events with NRT reported in uncontrolled studies: blood lipid levels*

Study details	Participant details	Results	Comments
Authors Moffat *et al.*, 2000[90] ***Study design*** Uncontrolled study ***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 criteria*** Not reported ***Baseline characteristics*** **Ex-smokers (*n* = 27):** Mean ± SD age: men, 45.3 ± 14.8 years; women, 38.2 ± 8.6 years Mean ± SD No. cigarettes/day: men, 29.2 ± 9.2; women, 28.6 ± 8.5 Mean ± SD No. years smoking: men, 25.7 ± 8.7; women, 19.7 ± 7.3 **Non-smokers (*n* = 16):** Mean ± SD age: men, 41.9 ± 11.1 years; women, 39.9 ± 10.8 years ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: Mean ± SD serum HDL-C/HDL2-C/HDL3-C (mg/dl), ex-smokers only – men: baseline, 36.0 ± 3.3/36.9 ± 3.4/42.6 ± 6.2, $p < 0.05$*; day 35, 10.2 ± 3.1/10.9 ± 3.0/15.5 ± 3.4, $p < 0.05$*; day 77, 25.6 ± 2.2/26.2 ± 2.4/27.0 ± 4.5 Mean ± SD serum HDL-C/HDL2-C/HDL3-C (mg/dl), ex-smokers only – women: baseline, 43.1 ± 6.0/42.9 ± 5.4/54.3 ± 6.5, $p < 0.05$*; day 35, 14.0 ± 2.9/14.2 ± 3.6/20.7 ± 3.6, $p < 0.05$*; day 77, 29.4 ± 5.8/28.7 ± 6.5/33.3 ± 6.4, $p < 0.05$* Mean ± SD body weight (kg) – men: baseline, 73.5 ± 8.0; day 35, 74.0 ± 7.7; day 77, 73.1 ± 9.0 Mean ± SD body weight (kg) – women: baseline, 65.3 ± 16.2; day 35, 65.7 ± 17.0; day 77, 67.4 ± 18.1, $p < 0.05$ compared to baseline Mean ± SD total cholesterol (mg/dl) – men: baseline, 197.0 ± 20.0; day 35, 197.6 ± 18.9; day 77, 199.7 ± 22.5 Mean ± SD total cholesterol (mg/dl) – men: baseline, 197.5 ± 35.0; day 35, 198.9 ± 36.6; day 77, 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**: NA	The authors note that the sample size is small (*n* = 43), and that their results conflict with those found in other studies

* *Significantly greater than baseline and day 35*

TABLE 48 *Adverse events with NRT reported in uncontrolled studies: abuse potential*

Study details	Participant details	Results	Comments
Authors Hatsukami *et al.*, 1993[82] ***Study design*** Uncontrolled study ***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 criteria*** Inclusions: 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 an 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	***Intervention*** **List of adverse events**: a checklist of withdrawal symptoms consisted of scores for craving, irritability/anger, anxiety/tension, difficulty concentrating, restlessness, somatic symptoms, hunger, impatience, insomnia, increased eating and drowsiness. The checklist was completed during the last 2 weeks of gum use and during the week following gum discontinuation. With 1 month's use of gum the mean ± SE scores were 13.6 ± 1.3 and 13.7 ± 1.5. With 3 month's gum use the 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 1-month and 3-month treatment groups. There was evidence of withdrawal symptoms (difficulty concentrating, increased variability in reaction-time tests and decreased vigour). The authors concluded that there is minimal physical dependence on nicotine gum **Comments**: NA	–
Authors Schuh *et al.*, 1997[91] ***Study design*** Uncontrolled study ***Specific intervention*** Nicotine nasal spray (0.5 mg/spray) and nicotine vapour inhaler (0.0013 mg/inhalation ***Comparator*** Nicotine from cigarette smoking (0.1 mg/puff) ***Duration of therapy*** 1 day ***Duration of follow-up*** 1 day	***Number of participants*** Intervention: *n* = 12 Comparator: *n* = 12 ***Inclusion/exclusion criteria*** Inclusions: smoked at least 20 cigarettes/day of a brand containing at least 0.7 mg nicotine/cigarette ***Participant characteristics*** Smokers who were deprived of nicotine overnight prior to testing Sex: 9/12 male Mean age: 36 years (range 21–45 years) Mean No. years of smoking: 18 (range 5–33) ***Proportion of participants reporting an adverse event*** Intervention: NA Comparator: NA	***Intervention*** **List of adverse events**: only modest elevations on a measure of good drug effects were observed with 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 the nasal spray or inhaler to produce 'good drug effects' and the unpleasant effects associated with them might be expected to limit the abuse liability **Comments**: NA	Overall results are consistent with the conclusion that the nicotine nasal spray and vapour inhaler are of substantially lower abuse liability than cigarettes in experienced smokers receiving initial exposure to these products

SE, standard error

TABLE 49 *Adverse events with NRT reported in case–control studies: incidence*

Study details	Participant details	Results
Authors Kimmel *et al.*, 2001[94] ***Study design*** Case–control study of association of myocardial with NRT patch use ***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 criteria*** Cases: smokers admitted to hospital with first myocardial infarction Controls: smokers who had not experienced a first myocardial infarction ***Baseline characteristics*** NA ***Proportion of participants reporting an adverse event*** NA	**List of adverse events**: only myocardial infarctions were studied. 3/653 cases had used a nicotine patch within the 7 days prior to their hospital admission for myocardial infarction (0.46%, compared with the patch use in controls of 30/2990 (1%); Exact OR = 0.46 (95% CI, 0.09 to 1.47)). This finding was adjusted for several confounders, but none of the adjustments had any real effect on the OR or the CIs **Comments**: this study did not identify a statistically or clinically significant association between the use of nicotine patches and myocardial infarction in an unselected population. The 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

TABLE 50 *Adverse events with NRT reported in surveillance studies*

Study details	Participant details	Results
Authors Spyker *et al.*, 1996[95] ***Study design*** Surveillance, post-marketing; information source, US Food and Drug Administration Spontaneous Reporting System for adverse events ***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 criteria*** NA ***Participant characteristics*** No details given ***Number of participants reporting an adverse event*** Intervention: 1281 (12.3/million patients treated) Comparator: 1281 (12.3/million patients treated)	***Intervention*** **List of adverse events**: a total of 3848 adverse events were reported with patch (11.8 adverse events/million patients treated). Dermatological (local or general), 1533 (130/million patients treated); addiction or dependence, 24 (2/million patients treated); gastrointestinal, hiccups, 522 (44/million patients treated); oral problems, 141 (12/million patients treated); withdrawal, no effect, headache, 442 (38/million patients treated); nervous system, central nervous system, 384 (33/million patients treated); sleep and dream disturbance, 416 (35/million patients treated) **Comments**: NA ***Comparator*** **List of adverse events**: a total of 3848 adverse events were reported with patch (11.8 adverse events/million patients treated). Dermatological (local or general), 39 (3.2/million patients treated); addiction or dependence, 475 (39/million patients treated); gastrointestinal, hiccups, 163 (13/million patients treated); oral problems, 289 (23/million patients treated); withdrawal, no effect, headache, 156 (13/million patients treated); nervous system, central nervous system, 75 (6.1/million patients treated); sleep and dream disturbance, 17 (1.4/million patients treated) **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 or data; no indication of dose regimens associated with adverse events; no participant details

continued

***TABLE 50* contd** *Adverse events with NRT reported in surveillance studies*

Study details	Participant details	Results
Authors Ottervanger *et al.*, 1997[96] ***Study design*** Surveillance (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) ***Specific intervention*** NA ***Comparator*** NA ***Duration of therapy*** NA ***Duration of follow-up*** NA	***Number of participants*** Not stated ***Inclusion/exclusion criteria*** Not reported ***Participant characteristics*** NA ***Number of participants reporting an adverse event*** Nine reports attributed to nicotine	***Intervention*** **List of adverse events**: total, 9 (8 with patches, 1 with gum). Myocardial infarction, 5; chest pain, 4. Nicotine was the second most frequently reported drug. Proportion of drug-induced myocardial infarction and chest pain attributed to nicotine, 4.1% **Comments**: study was designed to analyse causes of reported drug-induced myocardial infarction and chest pain rather than specifically to examine the incidence of these adverse events with NRT
Authors Spyker *et al.*, 1998[119] ***Study design*** Surveillance; source, US Food and Drugs Administration Medwatch Adverse Events Database ***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 and 11.8 million prescriptions for patches ***Inclusion/exclusion criteria*** Not reported ***Participant characteristics*** Not reported ***Number of participants reporting an adverse event*** Total of 5129 adverse event reports	***Intervention*** **List of adverse events**: site reactions, 29.7% of which were patch related and a further 24.1% of which were rashes, compared with 0.23% that were gum related and 1.17% which were rashes. All classes of adverse event were more common with patch than with gum, except for gum problems which were more common with gum. With patch: gastrointestinal-related events were three times more common; there were 18 times more allergy-related events; five times the number of nervous-system-related events; psychiatric events such as insomnia, dream abnormalities and nervousness were 30 times more frequent. Overall, patch was eight times was more likely to be associated with an adverse event than was gum **Comments**: spontaneous adverse event reports relating to nicotine patch and gum

TABLE 51 *Adverse events with NRT reported in systematic reviews*

Review details **Author**: Greenland *et al*., 1998[54] **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 P**articipants**: 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 (*n* = 34) (plus one study on contact sensitisation) **Type of smoker**: adults **Male/female ratio**: 1:1 **Level of nicotine dependence**: unclear **Fagerstrom score**: not stated **Specific intervention**: most studies used patches containing 17–25 mg nicotine. However, four studies (365 patients) used patches of 28 mg or more, ten studies (1793 patients) used patches of 14 or 15 mg, and two studies (167 patients) used patches of 7 or 8 mg **Comparator**: placebo. Usually this was completely inert but some studies (total of nine, 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 exhaustive in that it only included MEDLINE. It did, however, include published and unpublished studies from Ciba-Geigy. The cut-off date for papers to be included was 1 December 1996. So the data were not new

Appendix 7

Data extraction tables: adverse events with bupropion

TABLE 52 *Adverse events with bupropion reported in RCTs: cardiovascular events*

Study details	Participant details	Results	Comments
Authors Braconnier *et al.*, 1983[122] ***Study design*** RCT ***Specific intervention*** Bupropion 150 or 300 mg/day; high dose could be increased to 450 mg/day ***Comparator*** Imipramine 25 mg/day, could be increased to 150 mg/day ***Duration of therapy*** 28 days ***Duration of follow-up*** 28 days	***Number of participants*** Intervention: *n* = 90 (high dose, *n* = 45; low dose, *n* = 45) Comparator: *n* = 45 ***Inclusion/exclusion criteria*** Inclusions: age ≥ 55 years; 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): 63–64 years Sex: 45/110 male ***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, or orthostatic blood pressure of main effects on blood cholesterol **Comments**: findings agree with previous data that bupropion has no effect on cardiovascular 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-dose bupropion treatment ($p < 0.04$). No significant effect on PR or 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**: NA	–

continued

***TABLE 52* contd** *Adverse events with bupropion reported in RCTs: cardiovascular events*

Study details	Participant details	Results	Comments
Authors Kiev *et al.*, 1994[123] ***Study design*** RCT ***Specific intervention*** Bupropion, 225–450 mg/day (ascending regimen) ***Comparator*** Nortriptyline, 75–150 mg/day ***Duration of therapy*** 6 weeks ***Duration of follow-up*** Concurrent with period of treatment	***Number of participants*** Intervention: *n* = 58 Comparator: *n* = 57 ***Inclusion/exclusion criteria*** Inclusions: 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 Exclusions: 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; predisposition to seizures Medications prohibited during study: any psychoactive drug taken within 1 week of treatment phase (2 weeks for monoamine oxidase inhibitors or protriptyline and 4 weeks for fluoxetine or any investigational drug); prior therapy with bupropion or nortriptyline; current therapy with thyroid medication, cimetidine, quinidine, or other class I anti-arrhythmic agents ***Participant characteristics*** Mean age: 46.3 years Sex: 50% male ***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. Mean ± SD ECG changes from baseline: significant decrease of 47.9 ± 21.6 ms in mean RR interval on day 42 ($p < 0.05$), corresponding to a heart rate increase of 3.3 beats/min. 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 mmHg after 1 min standing, which was at least 20 mmHg 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 (mean ± SD, –188.2 ± 23.4 ms vs –47.9 ± 21.6 ms) and the QTC-interval (+14.4 ± 4.1 units vs. –6.4 ± 3.9 units) on day 42. Significant within-treatment difference ($p < 0.05$) on day 42 on the QRS interval duration (+4.4 ± 2.1 ms) Cardiovascular adverse events: dizziness, 1; oedema, 1; faintness, 2; palpitations, 2; tachycardia, 7 ($p < 0.05$ compared to bupropion) **Comments**: NA	Trial designed to compare safety of two antidepressants (bupropion and nortriptyline). Not conducted in the context of smoking cessation, hence population of psychiatric patients. Blood pressure and verbally reported patient experience were monitored weekly and ECGs taken at baseline (day 0), day 14 and day 42

continued

***TABLE 52* contd** *Adverse events with bupropion reported in RCTs: cardiovascular events*

Study details	Participant details	Results	Comments
Authors Roose *et al.*, 1987[124] ***Study design*** RCT ***Specific intervention*** Bupropion, 8 mg/kg; maximum dose 450 mg/day; mean ± SD daily dose 445 ± 16 mg (6.8 mg/kg) ***Comparator*** Imipramine, 3.5 mg/kg, to a maximum dose; mean daily dose 197 ± 78 mg (3 mg/kg) ***Duration of therapy*** 3 weeks ***Duration of follow-up*** Unclear	***Number of participants*** Intervention: *n* = 10 (1 dropout) Comparator: *n* = 9 (6 dropouts) ***Inclusion/exclusion criteria*** Inpatients of an affective-disorder ward requiring treatment with an antidepressant. All patients had a history of congestive heart failure with a large heart by chest roentgenogram (cardiothoracic ratio > 1 in the frontal view) ***Participant characteristics*** Sex: 6/10 female Mean age: 69 years (range 53–78 years) ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: Mean ± SD ejection fraction: baseline, 31 ± 13.7% (range 19–54%); post-bupropion, 32.4 ± 20.7% Mean ± SD end-diastolic volume: baseline103.5 ± 29.8; post-bupropion, 113.4 ± 40.3 Mean ± SD end-systolic volume (ESV): baseline, 72.4 ± 36.6; post-bupropion, 81.4 ± 43.9 Mean ± SD peak SBP/ESV: baseline, 2.36 ± 1.31; post-bupropion, 2.99 ± 2.92 Mean ± SD supine SBP: baseline, 132 ± 13 mmHg; post-bupropion, 136 ± 19 Mean orthostatic fall in blood pressure on bupropion: 2 mmHg Adverse events reported: chest pain (1 participant) **Comments**: bupropion did not have a deleterious effect on left ventricular function, nor did it induce orthostatic hypotension ***Comparator*** **List of adverse events**: Mean ± SD ejection fraction: baseline, 31 ± 13.7% (range 19–54%); post-bupropion, 30.4 ± 17.1 Mean ± SD end-diastolic volume: baseline, 103.5 ± 29.8; post-bupropion, 103.5 ± 37.5 Mean ± SD end systolic volume: baseline, 72.4 ± 36.6; post-bupropion, 76.2 ± 39.4 Mean ± SD peak SBP/ESV: baseline, 2.36 ± 1.31; post-bupropion, 2.53 ± 1.98 Mean ± SD supine SBP: baseline, 132 ± 13 mmHg; post-bupropion, 129 ± 16 Mean orthostatic fall in blood pressure on imipramine: 15 mmHg Adverse events reported by six participants: orthostatic hypotension (five participants); elevation of liver enzymes (one participant) **Comments**: NA	Study was of crossover design with drug tapering at the end of the first treatment and then a 5-day washout period before starting the second treatment. Study indicates that bupropion does not adversely effect left ventricular function

TABLE 53 *Adverse events with bupropion reported in RCTs: sexual functioning*

Study details	Participant details	Results	Comments
Authors Batey *et al.*, 1998[125] ***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 criteria*** Inclusions: outpatients with moderate to severe depression, in a stable relationship, with normal sexual functioning ***Participant 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**: NA ***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**: NA	Vital signs and weight assessments were comparable between the two treatment groups
Authors Coleman *et al.*, 1999[126] ***Study design*** RCT ***Specific intervention*** Bupropion SR, mean dose 290 mg/day (range 100–365 mg/day) ***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 criteria*** Inclusions: patients suffering from depression Exclusions: known predisposition to seizure or receiving medications that lower seizure threshold ***Participant characteristics*** Mean age: 38 years (range 18–74 years) Sex: 159/364 male ***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 Incidence of sexual arousal disorder was low: <1% at day 1, 6% at day 56; not statistically significantly different from placebo Orgasm dysfunction: 4% at day 7, 10% at day 56; 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 were tested using ANOVA. Attrition from the study was high (22% from bupropion group, 32% from placebo group, 36% from sertraline group). Difference primarily due to numbers lost to follow-up and contents withdrawn in different groups ***Comparator*** **List of adverse events**: the results for sertraline were not relevant, and were therefore not included Placebo: sexual arousal disorder was low (3% at day 1, 10% at day 56); orgasm dysfunction, 5% at day 7, 14% at day 56 (not statistically significantly different from placebo); premature ejaculation, 2–4% **Comments**: NA	Results suggest that bupropion has no adverse effect on sexual function in depressed participants

continued

***TABLE 53* contd** *Adverse events with bupropion reported in RCTs: sexual functioning*

Study details	Participant details	Results	Comments
Authors Labbate *et al.*, 2001[127] ***Study design*** RCT ***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 criteria*** Inclusions: healthy males ***Participant characteristics*** Mean ± SD age: 30.2 ± 6.3 years ***Proportion of participants reporting an adverse event*** Intervention: NA Comparator: NA	***Intervention*** **List of adverse events**: mean ± SD 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 ± 4.0; placebo, 44.8 ± 4.0; bupropion, 45.2 ± 3.2. There were no differences in any of the subscores during bupropion or placebo. 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. The aim of the study was to examine effects on penile erectile function, hence the reporting of loss of interest in smoking as an adverse event ***Comparator*** **List of adverse events**: see above **Comments**: NA	This was a randomised, placebo-controlled, crossover trial where all participants received both the interventions with a 7–10 day washout period between the two. Of the 16 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

continued

***TABLE 53* contd** *Adverse events with bupropion reported in RCTs: sexual functioning*

Study details	Participant details	Results	Comments
Authors Segraves *et al.*, 2000[128] ***Study design*** RCT ***Specific intervention*** Bupropion SR, 100–300 mg/day escalating dose ***Comparator*** Sertraline, 50–200 mg/day ***Duration of therapy*** 16 weeks ***Duration of follow-up*** Concurrent with study period	***Number of participants*** Intervention: *n* = 122 Comparator: *n* = 126 ***Inclusion/exclusion criteria*** Inclusions: minimum age 18 years; diagnosis of moderate to severe depression, duration 4 weeks to 24 months; patients were required to be in a stable relationship, have normal sexual functioning, perform sexual activity that could lead to orgasm at least once every 2 weeks, and be willing to discuss their sexual functioning with the investigator Exclusions: 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 week of study (2 weeks for MAOIs or protriptyline, and 4 weeks for fluoxetine or any investigational drug); prior use of bupropion or sertraline; actively suicidal ***Participant characteristics*** Sex, male: bupropion, 52%; sertraline, 52% Mean ± SD age: bupropion, 39 ± 10.5 years; sertraline, 40 ± 10.3 years (range 18–74 years) Mean compliance rate: bupropion, 98%; sertraline, 99% ***Proportion of participants reporting an adverse event*** Intervention: NA Comparator: NA	***Intervention*** **List of adverse events**: Sexual arousal disorder: men, 7%; women, 2% (p = 0.02 and 0.05, respectively, vs sertraline) Premature ejaculation: 5% (not significant vs sertraline) Orgasm dysfunction: men, 10%; women, 7% ($p < 0.001$ vs sertraline) **Comments**: study examined 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: men, 19%; women, 12% Premature ejaculation: 0% Orgasm dysfunction: men, 61%; women, 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

CSFQ, Changes in Sexual Functioning Questionnaire; LOCF, last observation carried forward; MAOI, monoamine oxidase inhibitor

TABLE 54 *Adverse events with bupropion reported in non-RCTs: cardiovascular events*

Study details	Participant details	Results	Comments
Authors Wenger *et al.*, 1983[129] ***Study design*** Non-RCT ***Specific intervention*** Bupropion, 300–750 mg, ascending regimen; mean maximum daily dose 552 mg ***Comparator*** Amitriptyline ***Duration of therapy*** 6 weeks ***Duration of follow-up*** NA	***Number of participants*** Intervention: *n* = 23 Comparator: *n* = 23 ***Inclusion/exclusion criteria*** Inclusions: depressed inpatients at a Veterans Administration Hospital ***Participant characteristics*** Sex: 100% male 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 the ECG parameters measured were: PR interval, 1.8 ± 1.7 ms; QRS duration, 0.4 ± 1.1 ms; QTC interval, –3.6 ± 3.5 ms; QRS height, 0.3 ± 0.4; RR interval, –30 ± 19 ms. None of these were statistically significant **Comments**: NA ***Comparator*** **List of adverse events**: significant prolongation in PR interval compared to that in participants; prolongation of QRS duration and decrease in QRS height compared to effect of bupropion **Comments**: NA	Data vs baseline suggests bupropion has little effect on cardiac conduction. Comparison with amitrypyline not relevent regarding smoking cessation

TABLE 55 *Adverse events with bupropion reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Roth and Westman, 1999[131] ***Study design*** Uncontrolled study ***Specific intervention*** Bupropion SR, 150 mg b.d. ***Comparator*** None ***Duration of therapy*** 8 weeks ***Duration of follow-up*** Unclear	***Number of participants*** *n* = 22 ***Inclusion/exclusion criteria*** Not reported ***Participant characteristics*** Sex: 96% male Mean ± SD age: 54 ± 10.1 years Mean ± SD No. cigarettes/day: 20.8 ± 13.0 64% had co-existing medical conditions: hypertension, coronary artery disease, chronic obstructive pulmonary disease 37% were receiving treatment for psychiatric diagnoses, including depression, post-traumatic stress disorder and bipolar disorder ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **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 bupropion SR 150 mg b.d.; it was resolved by reducing the dose to 150 mg/day **Comments**: –	Small sample size from which to make such general conclusions

continued

***TABLE 55* contd** *Adverse events with bupropion reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors van Wyck Fleet *et al.*, 1983[132] ***Study design*** Uncontrolled study (data pooled from clinical trials of bupropion) ***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 were not extracted as not a proper comparison) ***Duration of therapy*** 4–13 weeks (averages across studies) ***Duration of follow-up*** 4–13 weeks (averages across studies)	***Number of participants*** *n* = 1153 ***Inclusion/exclusion criteria*** Inclusions: those enrolled in clinical trials of bupropion (1970–1981); demonstrated normal and/or clinically acceptable values for physical examinations, vital signs, clinical laboratory test (haematology, clinical chemistry, urinalysis), EEG and a baseline evaluation of current symptomatology Exclusions: 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	***Intervention*** **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%; dermatological, 3.0%; nausea/vomiting, 2.7%; drowsiness, 2.6%; weight loss, 2.4%; headache/nasal congestion, 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: 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 were reported by two healthy volunteers and eight 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 (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 range was 600–900 mg/day, except for one patient with history of seizure who took 450 mg/day **Clinical significance**: – **Comments**: only adverse events that resulted in withdrawal of treatment were included in the summary. Also, given the relatively small size of the database, the cut-off of 2% for inclusion in this summary must mean many events were not included in this publication	–

continued

***TABLE 55* contd** *Adverse events with bupropion reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Davidson, 1989[133] ***Study design*** Uncontrolled study; data from previously conducted clinical trials ***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 criteria*** Not reported ***Participant characteristics*** 4097 patients, 165 volunteers ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **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 for which participants received the dose of bupropion at the dose at which the seizure occurred ranged from 1 to 281 days (mean 8 days), with 21 participants 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 **Clinical significance**: 11/1802 (0.61%) men suffered seizures compared with 23/2457 (0.93%) women (difference not significant). There was no association between seizure risk and age **Predisposing factors**: 14 patients were considered to have predisposing factors: a history of seizure (4, one with head trauma also), a history of metastatic brain carcinoma (1), undergoing alcohol withdrawal (1), head trauma (1), concomitant medication known to lower the seizure threshold (5), not stated (2) **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 mg/day, *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 weeks, *n* = 608; 27–52 weeks, *n* = 304; 53–104 weeks, *n* = 351; > 104 weeks, *n* = 239	–

continued

***TABLE 55* contd** *Adverse events with bupropion reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Peck *et al.*, 1983[181] ***Study design*** Uncontrolled retrospective cohort study ***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 criteria*** – ***Participant characteristics*** Inclusions: healthy participants or patients who experienced a convulsion during treatment or experiment with bupropion in North America ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: – **Clinical significance**: – **Comments**: summary of bupropion associated seizures	Exactly the same data as included in van Wyck Fleet *et al.*, 1983[132]

continued

***TABLE 55* contd** *Adverse events with bupropion reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Dunner *et al.*, 1998[134] ***Study design*** Uncontrolled cohort study (prospective, over 105 sites) ***Specific intervention*** Bupropion SR, 50–150 mg b.d. ***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 criteria*** Inclusions: 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 ***Participant characteristics*** Mean ± SD age: 42 ± 12 years (range 18–86 years) Sex: 1933/3100 female Major depression: 2304/3100 (74.3%) ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **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; two within the first 8 weeks. In this period the observed incidence rate was 0.06% (upper one-sided 95% CI, 0.14). The observed seizure rate for the whole study period (1 year) was 0.10% (upper one-sided 95% 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 one-sided 95% CI, 0.18) for the acute phase and 0.15% (upper one-sided 95% CI, 0.30) for the whole follow-up Other serious adverse events that were reported included: suicide attempt or overdose (9), accidental injury (4), myocardial infarction (3, all of whom had pre-existing cardiovascular pathology). There were also six deaths (3 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**: the doses of bupropion at which seizure occurred in three individuals were 300, 300 and 150 mg/day (4.2, 3.5 and 1.1 mg/kg, respectively) **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 two of the three cases: 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 confirming 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 nine reports of seizure, not three. Eight 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."

continued

***TABLE 55* contd** *Adverse events with bupropion reported in uncontrolled studies: incidence*

Study details	Participant details	Results	Comments
Authors Johnston *et al.*, 1991[135] ***Study design*** Uncontrolled cohort study ***Specific intervention*** Bupropion, 225–450 mg/day ***Comparator*** None ***Duration of therapy*** 8 weeks ***Duration of follow-up*** Unlimited	***Number of participants*** *n* = 3279 ***Inclusion/exclusion criteria*** Inclusions: minimum age 18 years; diagnosis of depression for which antidepressant treatment clinically appropriate Exclusions: 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 MAOI 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 ***Participant characteristics*** Sex: 1949/3279 female Mean ± SD age: 43.5 ± 3.2 years Major depression: 2391 Dysthymic disorder: 328 Bipolar depression: 271 Atypical depression: 190 Atypical bipolar disorder: 65 Other depressive diagnoses: 34 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **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; two at 375 mg/day and one at 300 mg/day. 10/13 occurred within 4 h of the last dose of bupropion, and 3/13 within 24 h. 3/13 seizures occurred within 14 days of starting bupropion therapy, 1/13 between days 15 and 21, four between days 29 and 56 and five after day 56. 4/13 seizures occurred within 1 week of a dose change Calculated observed seizure rate during the 56-day treatment phase was 0.24% (upper one-sided 95% CI, 0.38). Observed seizure rate for whole study was 0.40% (upper one-sided 95% CI, 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 (upper one-sided 95% CI, 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	–

b.d., twice daily; EEG, electroencephalogram

TABLE 56 *Adverse events with bupropion reported in uncontrolled studies: cardiovascular events (subjects with co-existing psychiatric disorders)*

Study details	Participant details	Results	Comments
Authors Farid *et al.*, 1983[136] ***Study design*** Uncontrolled study ***Specific intervention*** Bupropion, 50 mg tablets (100 mg t.d.s.) increasing to 600 mg/day as necessary (450 mg/day optimal for study) ***Comparator*** NA ***Duration of therapy*** 14 days, with, minimum of 7 days (450 mg/day) ***Duration of follow-up*** 14 days, concurrent with treatment	***Number of participants*** *n* = 12 ***Inclusion/exclusion criteria*** Inclusions: patients with a diagnosis of depression, receiving no neuroleptic, anxiolytic or other psychoactive drug for at least 1 week prior to the study (longer for certain drugs), and having a documented history of clinically significant tricyclic-induced orthostatic hypotension within the last 6 months ***Baseline characteristics*** Participants came from two centres (protocols run separately) Sex: 7/12 male Mean ages: 52 years and 57 years (overall range 36–65 years) ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: Variable mean ± SD supine SBP: placebo baseline, 126.9 ± 5.8 mmHg; after 14 days bupropion, 126.0 ± 6.4 mmHg Variable mean ± SD supine DBP: placebo baseline, 79.7 ± 3.5 mmHg; after 14 days bupropion, 76.3 ± 4.4 mmHg Variable mean ± SD standing SBP: placebo baseline, 120.4 ± 5.7 mmHg; after 14 days bupropion, 116.5 ± 4.8 mmHg Variable mean ± SD standing DBP: placebo baseline, 80.6 ± 3.6 mmHg; after 14 days bupropion, 80.2 ± 4.2 mmHg Variable mean ± SD supine minus standing SBP: placebo baseline, 6.5 ± 1.7 mmHg; after 14 days bupropion, 9.5 ± 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	–

continued

***TABLE 56* contd** *Adverse events with bupropion reported in uncontrolled studies: cardiovascular events (subjects with co-existing psychiatric disorders)*

Study details	Participant details	Results	Comments
Authors Roose *et al.*, 1991[137] ***Study design*** Uncontrolled study ***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 criteria*** Inclusions: inpatients with affective disorder needing treatment with antidepressants. Patients had chronic heart failure, enlarged heart, evidence of bundle branch block, defined as QRS interval > 0.10 s or more than 10 ventricular premature depolarisations/h determined by ECG ***Baseline characteristics*** Mean ± SD age: 69 ± 9 years Sex: 14/36 male Chronic heart failure: 15/36 Conduction disorder: 21/36 Ventricular arrhythmias (some with combination): 15/36 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: Variables measured at baseline and 3 weeks; statistical difference between treatments Mean ± SD pulse rate (beats/min): baseline, 74.8 ± 11.9; 3 weeks, 76.6 ± 10.4 (difference not significant) Mean ± SD ejection fraction (%) in participants with impaired left ventricular function (*n* = 15): baseline, 34 ± 13; 3 weeks, 2 ± 6% (difference not significant) Mean ± SD PR interval (s) in participants with pre-existing conduction disease (*n* = 21): baseline, 0.162 ± 0.02; 3 weeks, 0.167 ± 0.03 (difference significant at *p* = 0.06) Mean ± SD QRS interval in participants with pre-existing conduction disease (*n* = 21): baseline, 0.126 ± 0.01; 3 weeks, 0.128 ± 0.02 (difference not significant) No. of participants with ventricular premature depolarisation: baseline, 164 ± 133; 3 weeks, 69 ± 149 (difference significant at *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 atrioventricular block during treatment compared to baseline **Comments**: in addition to the specific safety issues looked at in this study, five participants dropped out due to adverse events: psoriasis and skin rash (1), increase of hypertension (2), orthostatic hypertension (1), history of coronary artery disease developed worsening of angina (1)	Discussion of cardiac effects of bupropion

t.d.s., three times daily

TABLE 57 *Adverse events with bupropion reported in uncontrolled studies: sexual function*

Study details	Participant details	Results	Comments
Authors Gardner and Johnston, 1985[139] ***Study design*** Uncontrolled study ***Specific intervention*** Flexible regimen of bupropion, 50–600 mg/day ***Comparator*** None ***Duration of therapy*** Up to 1 year ***Duration of follow-up*** Unclear	***Number of participants*** *n* = 40 ***Inclusion/exclusion criteria*** Not reported ***Baseline characteristics*** Age range: 20–60 years (one patient over 60 years old, exact age not stated) Major depression: 29/40 participants Bipolar disorder: 11/40 Duration of depression: range, 2–20 years Negative history of sexual dysfunction: 12 Positive history of sexual dysfunction: during antidepressant treatment only, 24; chronic history, 4; total positive history, 28 ***Proportion of participants reporting an adverse event*** NA	***Intervention*** ***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 years old. All 10 participants aged < 40 years improved their sexual functioning while receiving bupropion. The four patients who showed no change in their sexual dysfunction ranged in age from 50 to 67 years. Twelve patients with no history of sexual dysfunction reported normal sexual functioning **Comments**: none	Information supports lack of sexual dysfunction as a common side-effect of bupropion
Authors Rowland *et al.*, 1997[140] ***Study design*** Uncontrolled study ***Specific intervention*** Bupropion 75–150 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 criteria*** Inclusions: diabetic men aged 21–60 years, with erectile dysfunction (due to diabetes) ***Baseline characteristics*** Not reported ***Proportion of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: in this study there was no evidence that bupropion worsened or interfered 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. Physiological measures, such as penile brachial index and penile sensitivity, showed no overall change under bupropion. Autonomic function tests showed a decrease, but this was not statistically significant **Comments**: NA	–

TABLE 58 *Adverse events with bupropion reported in uncontrolled studies: body weight*

Study details	Participant details	Results	Comments
Authors Gardner, 1984[138] ***Study design*** Uncontrolled study ***Specific intervention*** Bupropion 50–600 mg/day (most common dose 300–450 mg/day) ***Comparator*** NA ***Duration of therapy*** Up to 1 year ***Duration of follow-up*** Up to 1 year	***Number of participants*** *n* = 58 ***Inclusion/exclusion criteria*** Inclusions: outpatients diagnosed with a non-psychotic 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	***Intervention*** **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 lb for men and –8.0 lb for women. Overall, 72% lost weight and 24% gained weight, with 4% showing no change. Changes in weight corresponded poorly with patients' reports of appetite suppression or increase **Comments**: NA	–

TABLE 59 *Adverse events with bupropion reported in survey-type studies: sexual function*

Study details	Participant details	Results	Comments
Authors Modell *et al.*, 1997[141] ***Study design*** Survey ***Specific intervention*** Bupropion (mean dose 276 mg/day, range 37.5–600 mg/day) ***Comparator*** Fluoxetine, 25 mg/day; paroxetine, 23 mg/day; or sertraline, 110 mg/day (all mean doses) ***Duration of therapy*** Mean ± SD, 4.8 ± 1.0 months ***Duration of follow-up*** NA	***Number of participants*** Intervention: *n* = 22 Comparator: fluoxetine, *n* = 37; paroxetine, *n* = 21; sertraline, *n* = 37 ***Inclusion/exclusion criteria*** Inclusions: 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 known to cause sexual side-effects; taking no other psychotrophic medication besides alprazolam or clonazepam ***Baseline characteristics*** Mean ± SD age: 41 ± 2.1 years Sex: 10/22 male Diagnosis of depression: 22 participants ***Proportion of participants reporting an adverse event*** Intervention: not reported Comparator: not reported	***Intervention*** **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, and duration and intensity of orgasm **Comments**: NA ***Comparator*** **List of adverse events**: all control drugs had reported detrimental effects on sexual functioning **Comments**: not relevant to smoking-cessation therapies	Small study. Attempts made to minimise potential effects of confounding factors and investigator bias

TABLE 60 *Adverse events with bupropion reported in surveillance studies*

Study details	Participant details	Results
Authors Therapeutic Goods Administration, 2001[142] ***Study design*** Surveillance; data from the Adverse Drug Reactions Advisory Committee (ADRAC), Australia ***Specific intervention*** Bupropion ***Comparator*** NA ***Duration of therapy*** NA ***Duration of follow-up*** NA	***Number of participants*** Not reported ***Inclusion/exclusion criteria*** Not reported ***Participant characteristics*** Not reported ***Number of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: 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/ angioedema, 62; chest pain, 54; shortness of breath, 38; increased sweating, 33; serum sickness, 33 **Comments**: authors state "ADRAC is satisfied, to date, that bupropion has not emerged as a cause of unexpected deaths."

continued

***TABLE 60* contd** *Adverse events with bupropion reported in surveillance studies*

Study details	Participant details	Results
Authors Hebert, 1999[143] ***Study design*** Surveillance ***Specific intervention*** Bupropion SR, used as licensed as Zyban only ***Comparator*** None ***Duration of therapy*** Unclear ***Duration of follow-up*** 18 August to 1 December 1998	***Number of participants*** Not stated ***Inclusion/exclusion criteria*** Inclusions: people trying to stop smoking; drug used as licensed ***Participant characteristics*** Mean age: 36 years (range 27–81 years) ***Number of participants reporting an adverse event*** Total of 48 reports of adverse reactions to bupropion (15 men, 31 women, 2 unknown)	***Intervention*** **List of adverse events**: the 48 reports included a total of 144 adverse reactions. Grouped by body system, these were as below Central and peripheral nervous system: tremor (6), dizziness (5), hypoaesthesia (3), stupor (3), paralysis (2), grand mal convulsions (2), coordination abnormality (2), hyperkinesia (2), dyskinesia (1), dysaesthesia (1), vertigo (1), speech disorder (1), headache (1), convulsions (1), paraesthesia (1) Dermatological: pruritus (9), urticaria (7), rash (4), erythematous rash (4), erythema multiforme (2), Stephens–Johnson syndrome (1), maculopapular rash (1), skin discoloration (1) Body: oedema (7), chest pain (3), face oedema (2), allergic reaction (2), malaise (2), fatigue (2), fever (1), condition aggravated (Bell's palsy) (1), asthenia (1), sensation of warmth (1), cold extremities (1), peripheral oedema (1), mouth oedema (1), pharynx oedema (1) Psychiatric: insomnia (5), anxiety (5), suicide ideation (3), hallucination (3), aggressive reaction (1), anorexia (1), paranoia (1), confusion (1), depression (1), nervousness (1), impaired concentration (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) Ophthalmic: abnormal vision (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**: NA

continued

***TABLE 60* contd** *Adverse events with bupropion reported in surveillance studies*

Study details	Participant details	Results
Authors Medicines Control Agency, 2001[97] ***Study design*** Surveillance ***Specific intervention*** Bupropion ***Comparator*** NA ***Duration of therapy*** NA ***Duration of follow-up*** NA	***Number of participants*** Estimated 390,000 patients ***Inclusion/exclusion criteria*** Inclusions: persons treated for smoking cessation as per the UK Product Licence for bupropion SR ***Participant characteristics*** Not reported ***Number of participants reporting an adverse event*** NA	***Intervention*** **List of adverse events**: total 5593 events. Urticaria, 761; insomnia, 761; rashes, 724; headache, 537; dizziness, 534; nausea, 489; angioedema, 348; depression, 345; tremor, 279; pruritus, 283; anxiety, 232; chest pain, 238; dry mouth, 189; dyspnoea, 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 number); 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 were not necessarily caused by the drug

TABLE 61 *Adverse events with bupropion reported in systematic reviews*

Review details **Author**: Holm and Spencer, 2000[13]
Objective: to review the use of bupropion SR in the management of smoking cessation
Inclusion criteria: –
Study design: any; precedent given to large, well-controlled trials, with appropriate statistical methodology
Participants: using bupropion SR for smoking cessation
I**ntervention**: 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 adverse events data, there were three RCTs, two prospective safety studies, one retrospective study and several case reports
Type of smoker: adults
Male/female 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: –
Comments –

Appendix 8

Quality assessment of included studies

TABLE 62 *Quality assessment of RCTs*

Study	Random allocation	Method of allocation	Adequate concealment	No. of patients randomised	Comparable at baseline	Co-interventions	Inclusion/exclusion criteria	Patients blinded	Assessors blinded	Success of blinding checked	80% followed up	Reasons for withdrawals	ITT analysis
Allen *et al.*, 1995[60]	Yes	Not stated	Yes	No	Unclear	–	Yes	Yes	Yes	No	Yes	Yes	Unclear
Batey *et al.*, 1998[125]	Yes	Not stated	Unclear	Yes	Unclear	No	Yes	No	No	No	Unclear	No	Unclear
Braconnier *et al.*, 1983[122]	Unclear	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Unclear
Clavel-Chapelon *et al.*, 1997[28]	Yes	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	Yes	Yes	Yes
Coleman *et al.*, 1999[126]	Yes	Not stated	Yes	Yes	Yes	None reported	Yes	Yes	Yes	No	No	Yes	Yes
Epifano *et al.*, 1992[63]	Yes	Not stated	Unclear	Yes	Yes	None reported	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear
Fishbein *et al.*, 2000[56]	Yes	Not stated	No	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
GlaxoSmithKline, 1999[33*]	–	–	–	–	–	–	–	–	–	–	–	–	–
GlaxoSmithKline, 1999[44*]	–	–	–	–	–	–	–	–	–	–	–	–	–
GlaxoSmithKline, 2001;[45*] Gonzales *et al.*, 2001[49]	Yes	Randomised codes	Yes	Yes	Unclear	No	Yes	Yes	Yes	No	No	No	Yes
GlaxoSmithKline, 2000[34*]	–	–	–	–	–	–	–	–	–	–	–	–	–
GlaxoSmithKline, 1999[43*]	–	–	–	–	–	–	–	–	–	–	–	–	–
Hardardottir *et al.*, 1996[120]	Yes	Not stated	Unclear	Yes	Unclear	None stated	Yes	No	Unclear	No	No	Unclear	Unclear
Hertzberg *et al.*, 2001[53]	Yes	Not stated	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear
Hurt *et al.*, 1995[67]	Yes	Not stated	Unclear	Yes	Unclear	None reported	Yes	Unclear	Unclear	No	Yes	Yes	Yes
Jensen *et al.*, 1991[27]	Yes	Block randomisation	–	No	Yes	No	Yes	No	No	No	Yes	No	Yes
Jordan, 1992[68]	Yes	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Unclear	Unclear
Joseph *et al.*, 1996[55]	Yes	Computer generated	Yes	Yes	Yes	No	Yes	Yes	Unclear	No	No	Unclear	Yes
Keeley *et al.*, 1996[62]	Yes	Not stated	Unclear	Yes	Unclear	None reported	Yes	Unclear	Unclear	No	Yes	Yes	Unclear
Khoury *et al.*, 1996[64]	Yes	Not stated	Unclear	Yes	Yes	None reported	Yes	Yes	Yes	No	Yes	Yes	Unclear

continued

TABLE 62 contd *Quality assessment of RCTs*

Study	Random allocation	Method of allocation	Adequate concealment	No. of patients randomised	Comparable at baseline	Co-interventions	Inclusion/exclusion criteria	Patients blinded	Assessors blinded	Success of blinding checked	80% followed up	Reasons for withdrawals	ITT analysis
Kiev *et al.*, 1994[123]	Yes	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Unclear	Unclear	Unclear
Labbate *et al.*, 2001[127]	Yes	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	Yes	Yes	No
Lucini *et al.*, 1998[57]	Yes	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Unclear
Neunteufl *et al.*, 2001[58]	Yes	Not stated	Unclear	Yes	Unclear	No	No	No	Yes	No	Unclear	NA	NA
Nordstrom *et al.*, 1999[69]	Yes	Not stated	Yes	Yes	Yes	–	Yes	Yes	Unclear	No	Yes	Unclear	Unclear
Oncken *et al.*, 1997[71]	Yes	Computer generated	Unclear	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No
Roose *et al.*, 1987[124]	Yes	Not stated	Unclear	Yes	Yes	–	Yes	No	No	No	Yes	Yes	Unclear
Sahba *et al.*, 2000[61]	Yes	Not stated	Unclear	Yes	Yes	–	Yes	Yes	Unclear	No	Yes	–	–
Sawe, 1997[443]	Yes	Computer generated	Yes	Yes	Yes	None reported	Yes	Yes	Yes	No	No	Yes	Unclear
Segraves *et al.*, 2000[128]	Yes	Not stated	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	Incomplete	No
Settle *et al.*, 1999[449]	Unclear	Not stated	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear
Solomon *et al.*, 2000[30]	Yes	Not stated	Unclear	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes
GlaxoSmithKline, 2000[32]	Yes	Computer generated/ block randomisation	Yes	Yes	Yes	Not stated	Yes	Yes	Yes	No	No	Yes	Yes
Tashkin *et al.*, 2001[46]	Yes	Block randomisation	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	No	Yes	Yes
Tzivoni *et al.*, 1996[66]	Yes	Not stated	Yes	Yes	Unclear	None reported	Unclear	Yes	Yes	No	Unclear	No	Unclear
Tzivoni *et al.*, 1998[117]	Unclear	Not stated	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes
West *et al.*, 2000[70]	Yes	Not stated	Unclear	Yes	Unclear	–	Yes	No	No	No	Unclear	Unclear	
Wisborg *et al.*, 2000[31]	Yes	Randomisation list and code	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wong *et al.*, 1999[29]	Yes	Computer generated	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes
Working Group for the Study of Transdermal Nicotine in Patients with CAD, 1994[59]	Yes	Block randomisation	Yes	Yes	Yes	–	Yes	Yes	Yes	No	Yes	Unclear	Yes

continued

TABLE 63 *Quality assessment of non-RCTs*

Study	Random allo-cation	Method of allocation	Adequate conceal-ment	No. of patients recruited	Compar-able at baseline	Co-interventions	Inclusion/ exclusion criteria	Patients blinded	Assessors blinded	Success of blinding checked	80% followed up	Reasons for with-drawals	ITT analysis
Benowitz *et al.*, 1993[74]	No	Not stated	Unclear	Yes	Yes	No	Yes	Yes	Unclear	No	Yes	Unclear	Unclear
Netscher *et al.*, 1995[72]	No	Crossover study	No	No	Yes	None stated	Yes	No	No	No	Yes	Unclear	Unclear
Wenger *et al.*, 1983[129]	No	Unclear	Unclear	No	Unclear	None stated	No	Yes	Yes	No	Unclear	Unclear	Unclear
Zevin *et al.*, 1998[73]	No	Crossover study	No	Yes	Yes	None stated	Yes	No	No	No	–	None	Yes

ITT, intention-to-treat

* *Trials removed for reasons of commercial confidentiality. The results of these individual studies have not been included in the review*

TABLE 64 *Quality assessment of uncontrolled studies*

Study	Group clearly stated	Control group	If no control, OK?	Follow-up adequate	Aims	Study design appropriate	Sample size appropriate	Valid measurements	Valid outcome measurements	All patients accounted for	Are statistics well described?	Statistics appropriate
Bende *et al.*, 1998[78]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	NA	NA
Bircher *et al.*, 1991[84]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	NA	NA
Bjornson-Benson *et al.*, 1993[79]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA
Davidson, 1989[133]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Dunner *et al.*, 1998[134]	Yes	No	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Farid *et al.*, 1983[136]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	No	Yes
Fredrickson *et al.*, 1995[75]	Yes	No	No	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes
Gardner, 1984[138]	Yes	No	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Gardner and Johnston, 1985[139]	Yes	No	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear
Girdler *et al.*, 1997[300]	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Gourlay *et al.*, 1999[76]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear
Hatsukami *et al.*, 1993[82]	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Unclear	Unclear
House *et al.*, 1995[80]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	NA	NA
Hurt *et al.*, 1998[77]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Johnston *et al.*, 1991[135]	Yes	No	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Unclear
Krivokapich *et al.*, 1984[65]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Mahmarian *et al.*, 1997[88]	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Murray *et al.*, 1996[381]	Yes	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Unclear	No	Yes
McNabb, 1984[81]	Yes	Yes	NA	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	NA	NA
Mills *et al.*, 1997[85]	Yes	No	Unclear	No	Unclear	Unclear	No	Unclear	Unclear	Yes	NA	NA
Moffat *et al.*, 2000[90]	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Nitenberg and Antony, 1999[89]	Yes	No	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Ogburn *et al.*, 1999[92]	Yes	No	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Roose *et al.*, 1991[137]	Yes	No	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	Unclear
Roth and Westman, 1999[131]	Yes	No	Unclear	No	Yes	No	No	Unclear	Yes	Unclear	–	–

continued

***TABLE 64* contd** *Quality assessment of uncontrolled studies*

Study	Group clearly stated	Control group	If no control, OK?	Follow-up adequate	Aims	Study design appropriate	Sample size appropriate	Valid measurements	Valid outcome measurements	All patients accounted for	Are statistics well described?	Statistics appropriate
Rowland *et al.*, 1997[140]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear
Sarabi and Lind, 2000[86]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Schuh *et al.*, 1997[91]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Stein *et al.*, 1996[87]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
van Wyck Fleet *et al.*, 1983[132]	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Wallstrom *et al.*, 1999[83]	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Zevin *et al.*, 1998[73]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	NA	NA

TABLE 65 *Quality assessment of case–control studies*

Study	**Kimmel *et al.*, 2001[94]**
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
Study design appropriate?	Yes
Sample size appropriate?	Unclear
Measurements valid and reliable?	Yes
Were the outcome measures appropriate?	Yes
Were 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

TABLE 66 *Quality assessment of survey-type studies*

Study	**Aims clearly stated?**	**Population studies appropriate?**	**Statistical methods well described?**	**Statistical methods appropriate?**	**Was there risk of significant bias?**
Modell *et al.*, 1997[141]	Yes	Yes	Yes	Yes	Unclear

TABLE 67 *Quality assessment of surveillance studies*

Study	**Source of data clearly stated**	**Population appropriate**	**Any specific data not included**	**Statistics performed on the database appropriate**	**Statistics well described**	**Statistical methods appropriate**
Therapeutic Goods Administration, 2001[142]	Yes	Yes	No	Yes	NA	NA
Hebert, 1999[143]	Yes	Yes	No	NA	NA	NA
Medicines Control Agency, 2001[97]	Yes	Yes	No	Yes	NA	NA
Ottervanger *et al.*, 1997[96]	Yes	Yes	Unclear	NA	NA	NA
Preskorn, 1995[415]	Unclear	Unclear	No	NA	NA	NA
Spiller *et al.*, 1994[465]	Yes	Unclear	Yes	Yes	Yes	Yes
Spyker *et al.*, 1996[95]	Yes	Yes	Unclear	Unclear	No	Unclear
Spyker *et al.*, 1998[119]	Yes	Yes	Unclear	Yes	Unclear	Unclear

TABLE 68 *Quality assessment of systematic reviews*

	Study				
	Fiore *et al.*, 2000[25]	**Greenland *et al.*, 1998[54]**	**Holm and Spencer, 2000[13]**	**Hughes *et al.*, 2000[42]**	**Silagy *et al.*, 2001[26]**
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	✔	✗	✗	✗	✔
Valid inclusion/exclusion criteria	✔	✔	✔	✔	✔
Validity systematically assessed	✗	✗	✗	✔	✔
Validity criteria applied by more than one author	✗	✗	✗	✗	✔
Validity taken into account in synthesis	✗	✗	✗	✗	✗
Data extraction performed by more than one author	✔	✗	✗	✔	✔
Primary studies are presented in sufficient detail	✗	✔	✔	✔	✔
Primary studies have been synthesised appropriately	✔	✔	✔	✔	✔
Meta-analysis has been performed	✔	✔	✗	✔	✔
If 'Yes', has heterogeneity been formally assessed?	✔	✔	✗	✔	✔

Appendix 9

Case reports and case series included in the review

TABLE 69 *Case reports and case series: NRT*

Study	Intervention details	Patient details	Adverse event(s)
Brandspigel and Walsh, 1987[100]	Nicotine gum **Concomitant medication**: none reported	32-year-old male diagnosed with a duodenal ulcer	Severe vomiting
Dousset *et al.*, 1986[101]	Nicotine gum (20 mg nicotine) **Concomitant medication**: none reported	29-year-old male	Increase in serum triglycerides and cholesterol
Einarson and Einarson, 1997[102]	Nicotine gum (Nicorette, 2 mg) **Concomitant medication**: hydrochlorothiazide/triamterene	51-year-old female smoker (8 cigarettes/day)	Abrupt, forceful hiccups, 15 min in duration
Farm, 1993[103]	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. While using the nicotine gum, symptoms worsened
Foulds and Toone, 1995[104]	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 while wearing the patch	Suspected nicotine intoxication. Patient awoke feeling dizzy, nauseous and weak. Suffered delusions and hallucinations
Frazier *et al.*, 1993[105]	Nicotine patch (ProStep, 14 mg) **Concomitant medication**: none reported	31-year-old female	Swelling of feet, legs, hands, face and throat and a blister-like rash under the adhesive
Goodman and Douglas, 1987[106]	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 min after chewing a piece of gum. The rash completely disappeared when the patient stopped chewing the gum
Jackson, 1993[107]	Nicotine patch (Nicotinell TTS 30, 30 mg) **Concomitant medication**: none reported	62-year-old female	After 3 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 *et al.*, 1994[108]	Nicotine patch (Nicopatch, 30 cm^2) **Concomitant medication**: none reported	47-year-old male	Patient was stung on patch site by a wasp. Developed an anaphylactoid reaction

continued

***TABLE 69* contd** *Case reports and case series: NRT*

Study	Intervention details	Patient details	Adverse event(s)
Moreau *et al.*, 1997[109]	Nicotine patch (Nicotinell, 21 mg/24 h) **Concomitant medication**: none reported	48-year-old male smoker (40 cigarettes/day) suffering from myasthenia gravis	Symptoms of myasthenia gravis became more severe
Ottervanger *et al.*, 1995[110]	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[111]	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 *et al.*, 1993[112]	Nicotine patch (30 mg) **Concomitant medication**: none reported	33-year-old male smoker (30 cigarettes/day)	Tachyarrythmia, loss of consciousness and agitation upon application of the patch
Stewart and Catterall, 1985[113]	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 *et al.*, 1993[114]	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 burning sensation
von Bahr and Wahlberg, 1997[115]	Nicotine patch **Concomitant medication**: none reported	46-year-old female, heavy smoker	Itch and erythema appeared, persisting for several days
Warner and Little, 1994[116]	Nicotine patch (21 mg) **Concomitant medication**: none reported	47-year-old male smoker who had previously suffered an inferior myocardial infarction	Patient smoked while continuing to wear the patch and developed severe chest pain. Diagnosed with a myocardial infarction

TABLE 70 *Case reports and case series: bupropion*

Study	Intervention details	Patient details	Adverse event(s)
Amann *et al.*, 2000[145]	Bupropion SR (300 mg/day) **Concomitant medication**: lamotrigine and olanzapine	38-year-old female diagnosed with schizoaffective disorder	Hypesthesia of two branches of the left trigeminal nerve. Perception of touch and pain appeared impaired
Ames *et al.*, 1992[146]	**Case 1**: bupropion (150 mg b.d.) **Case 2**: bupropion (300 mg/day) **Case 3**: bupropion (75 mg b.d.) **Concomitant medication** **Case 1**: lithium carbonate, clonazepam, propanolol and temazepam **Case 2**: lithium carbonate and cimetidine **Case 3**: none reported	**Case 1**: 63-year-old male with anergic non-psychotic depression **Case 2**: 50-year-old male with a history of bipolar illness **Case 3**: 23-year-old female with a history of intermittent 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[147]	Bupropion (150 mg/day) **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 and Young, 1991[148]	Bupropion (75 mg/day) **Concomitant medication**: diltiazem	78-year-old male with history of recurrent major depression	Patient developed mania
Dager and Heritch, 1990[149]	Bupropion (375 mg/day) **Concomitant medication**: lithium carbonate and propanolol	48-year-old male with a history of bipolar illness	Patient suffered from delirium
David, 1999[150]	Bupropion (150 mg b.d) **Concomitant medication**: glipizide and metformin	49-year-old male with post-traumatic stress disorder and type II diabetes	Patient was found to suffering from rhabdomyolysis associated with hepatic dysfunction
Fichtner *et al.*, 1992[151]	Bupropion (100 mg t.d.s.) **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[152]	Bupropion (225 mg/day) **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 *et al.*, 1985[153]	**Case 1**: bupropion (500 mg/day) **Case 2**: bupropion (300 mg/day) **Case 3**: bupropion (425 mg/day) **Case 4**: bupropion (100 mg/day) **Concomitant medication** **Cases 1, 3 and 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

continued

***TABLE 70* contd** *Case reports and case series: bupropion*

Study	Intervention details	Patient details	Adverse event(s)
Goren and Levin, 2000[154]	Bupropion (600 mg/day) **Concomitant medication**: gabapentin	44-year-old male suffering from bipolar affective disorder	Patient experienced a manic episode
Halbreich *et al*., 1991[155]	**Case 1**: bupropion (450 mg/day) **Case 2**: bupropion (450 mg/day) **Concomitant medication**: none reported	**Case 1**: 30-year-old female with history of major depressive disorder (melancholic type), post-partum depression and migraine headaches **Case 2**: 28-year-old female with diagnosis of major depressive disorder (melancholic type)	**Case 1**: shortened menstrual cycle marked by heavy, prolonged menstrual bleeding **Case 2**: shortened menstrual cycle and irregularities
Howard and Warnock, 1999[156]	Bupropion (100 mg t.d.s.) **Concomitant medication**: ibuprofen, sucralfate, colchicine and betaxolol hydrochloride ophthalmic solution	79-year-old male diagnosed with an initial episode of severe major depression following a suicide attempt	Paranoia and auditory hallucinations
Hu *et al*., 2000[157]	Bupropion (200 mg/day) **Concomitant medication**: none	41-year-old male with history of chronic hepatitis C and major depression	Acute hepatitis
Humma and Swims, 1999[158]	Bupropion (100 mg t.d.s.) **Concomitant medication**: captopril, metoprolol, furosemide, cimetidine, diltiazem, aspirin, 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, hyperlipidaemia, peptic ulcer disease and chronic obstructive pulmonary disease	Diagnosed with presumptive transient ischaemic attacks
Jackson *et al*., 1992[159]	Bupropion (75 mg t.d.s.) **Concomitant medication**: none reported	19-year-old male suffering from depression	Catatonia; patient became withdrawn and unresponsive
Kanani *et al*., 2000[160] (abstract)	Bupropion SR (dose not reported) **Concomitant medication**: none reported	Not reported	Four cases of serum-sickness-like reaction
Labbate, 1998[161]	Bupropion SR (150 mg t.d.s.) **Concomitant medication**: none reported	37-year-old male with history of attention-deficit disorder	Increased libido and spontaneous erections
Levenson, 1995[162]	Bupropion (100 mg b.d.) **Concomitant medication**: none reported	50-year-old female with major depression and irritable syndrome	Clitoral priapism and prolonged sexual arousal; discontinuation of bupropion resulted in the spontaneous resolvement of the priapism and arousal
Liberzon *et al*., 1990[163]	Bupropion (75 mg b.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

continued

***TABLE 70* contd** *Case reports and case series: bupropion*

Study	Intervention details	Patient details	Adverse event(s)
Mainie *et al.*, 2001[164]	Overdose of bupropion (3.75 g) **Concomitant medication**: none	19-year-old healthy female	Two brief generalised seizures; was discharged from hospital the next day
Malesker *et al.*, 1995[165]	Bupropion (100 mg b.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 and Stern, 1993[166]	Bupropion (up to 350 mg/day) **Concomitant medication**: phenazine	36-year-old female with short history of depression (with psychotic features)	Patient developed a manic syndrome
McCollum *et al.*, 2000[167]	Bupropion (dose not reported) **Concomitant medication** **Cases 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, characterised by a pruritic skin rash **Case 2**: presumed allergic reaction to bupropion **Case 3**: pruritic rash and arthalgias
Patten *et al.*, 1999[169]	**Case 1**: bupropion (150 mg/day) **Cases 2 to 5**: bupropion (300 mg/day for 7 weeks), then bupropion or placebo **Concomitant medication**: none reported	**Case 1**: 45-year-old female smoker (25 cigarettes/day) with a history of one major depressive episode **Case 2**: 54-year-old female smoker (20 cigarettes/day) with a history of one major depressive episode **Case 3**: 35-year-old female smoker (20 cigarettes/day) **Case 4**: 55-year-old female smoker (30 cigarettes/day) with a history of two previous episodes of depression **Case 5**: 44-year-old male smoker (20 cigarettes/day) with a history of one 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 irritability 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
Paris *et al.*, 1998[168]	Overdose of bupropion (9 g) **Concomitant medication**: none reported	32-year-old healthy male	Patient was agitated and tremulous and developed a grand mal seizure
Peloso and Baillie, 1999[170]	Bupropion (300 mg/day) **Concomitant medication**: none reported	21-year-old male	Allergic reaction to bupropion, characterised by diffuse achiness of the shoulders and hips on day 10, and on subsequent days diffuse swelling of the fingers, toes, knees and eyelids
Ramasubbu, 2000[171]	Bupropion SR (300 mg/day) **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

continued

***TABLE 70* contd** *Case reports and case series: bupropion*

Study	Intervention details	Patient details	Adverse event(s)
Settle, 1991[172]	**Case 1**: bupropion (450 mg/day) **Case 2**: bupropion (100 mg t.d.s.) **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 *et al.*, 1986[173]	Bupropion (600 mg/day) **Concomitant medication**: none reported	25-year-old female with a history of chronic anxiety accompanied by panic attacks and phobias	Generalised convulsion with tonic and clonic phases, loss of consciousness and post-ictal confusion
Szuba and Leuchter, 1992[174]	**Case 1**: bupropion (400 mg/day) **Case 2**: bupropion (450 mg/day) **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 and Greenberger, 1999[175]	Bupropion (300 mg/day) **Concomitant medication**: none reported	44-year-old healthy female	Serum-sickness-like reaction; patient developed arthralgias, myalgias, fatigue, and fevers and chills
van Putten and Shaffer, 1990[176]	Bupropion (300 mg/day) **Concomitant medication**: fluoxetine	41-year-old male suffering from non-psychotic anergic depression	Patient developed "myoclonic jerking", and became severely agitated and psychotic
Workman and Short, 1992[177]	Bupropion (100 mg t.d.s.) **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-lb
Yolles *et al.*, 1999[178]	Bupropion SR (150 mg/day) **Concomitant medication**: olanzapine, lithium carbonate and levothyroxine	45-year-old male diagnosed with recurrent depression with psychotic features and schizo-affective disorder (depressed type)	Drug hypersensitivity reaction; 5 days after the introduction of bupropion the patient developed a high temperature, joint and chest pain, and a rash
Zubieta and Demitrack, 1991[179]	Bupropion (200 mg/day) **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

Appendix 10

Data extraction table: economic evaluations

TABLE 71 *Data extraction tables: economic evaluations*

Study; participants	Interventions, estimated cessation rates; methods	Methods for estimating LYS or QALYs; adjusting factor	Categories of costs considered	Viewpoints; discount rate; dealing with uncertainty	Results	Authors' conclusions; commentary
Parrott *et al.*, 1998,[23] UK Participants: a health authority with the national average population of 500,000 and national smoking rates	Brief advice: 3% Above + self-help material: 4% Above + NRT: 6% Above + specialist service: 10% without NRT; 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	Viewpoints: 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 interventions
Orme *et al.*, 2001,[185] UK Participants: a cohort of UK smokers	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	Viewpoints: 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 healthcare costs Reviewers' comments: the model is easy to use
Akehurst and Piercy, 1994,[182] UK Participants: smokers aged ≥ 20 years; 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	Viewpoints: 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 NRT patches in addition to GP counselling represents good value for money in comparison with other accepted health interventions

continued

TABLE 71 contd *Data extraction tables: economic evaluations*

Study; participants	Interventions, estimated cessation rates; methods	Methods for estimating LYS or QALYs; adjusting factor	Categories of costs considered	Viewpoints; discount rate; dealing with uncertainty	Results	Authors' conclusions; commentary
Akehurst and Piercy, 1994,[183] UK Participants: heavy smokers (> 23 cigarettes/day)	GP counselling: 3.7% Counselling + NRT nasal spray: 26.0% (16% used in sensitivity analysis) Spontaneous quit rate: 1% Relapse rate: 0% (Based on results of an 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: 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 LYS by a programme of counselling plus use of Nicorette nasal spray in heavy smokers compares favourably with other NHS interventions at around £1430/LYS
Stapleton *et al.*, 1999,[186] UK Participants: dependent smokers (> 14 cigarettes/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[198] study of a cohort of male GPs LYS/quitter according to age of quitting: < 35 years, 1.69; 35–44 years, 1.94; 45–54 years, 1.55; 55–65 years, 1.08 (Note: number of quitters without relapse)	GP or nurse time; costs of NRT; booklets; biochemical validation	Viewpoints: 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 years old, £398/LYS; 35–44 years old, £345/LYS; 45–54 years old, £432/LYS; 55–65 years old, £785/LYS (Reference: GP advice only)	The low cost per LYS would make GP intervention against smoking a cost-effective life-saving treatment Commentary: ACT model – abstinence contingent treatment; used data from a trial and a survey of associated resource use in 30 GPs
Crealey *et al.*, 1998,[184] 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)	Based on life-expectancies of smokers vs non-smokers in the USA LYS/quitter according to age of quitting: 35–44 years, men 1.5, women 0.7; 45–54 years, men 2.0, women 1.1; ≥ 55, men 2.4, women 2.1	PAS materials; pharmacists' training and time Costs of NRTs not considered; paid for by smokers	Viewpoints: NHS Discount rate: costs not discounted; health benefits, 4% Sensitivity analysis	(UK £, 1997) PAS programme: £509/quitter (depending on age group); men £197–351/LYS; women £181–772/LYS (Reference: no PAS programme)	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

continued

***TABLE 71* contd** *Data extraction tables: economic evaluations*

Study; participants	Interventions, estimated cessation rates; methods	Methods for estimating LYS or QALYS; adjusting factor	Categories of costs considered	Viewpoints; discount rate; dealing with uncertainty	Results	Authors' conclusions; commentary
Cromwell *et al.*, 1997,[187] USA Population: adult smokers (> 18 years old) in the USA	Minimal counselling: 5.9% Minimal counselling + NRT patch: 11.7% Minimal counselling + NRT gum: 8.7% Brief counselling: 6.9% Brief counselling + NRT patch: 13.4% Brief counselling + NRT gum: 10.0% Full counselling: 11.2% Full counselling + NRT patch: 21.0% Full counselling + NRT gum: 15.9% Intensive counselling: 11.6% Intensive counselling + NRT patch: 21.6% Intensive counselling + NRT gum: 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 and Franks, 1996[188] LYS/quitter: 1.46 QALYS/quitter: 1.97 (Note: number of quitters after relapse)	Costs of physicians for screening, advising and motivating; direct costs of interventions (educational materials, NRTs)	Viewpoints: 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 + NRT patch: $2310–4745/quitter; $1581–3248/LYS; $1171–2405/QALYS Counselling + NRT gum: $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 QALYS, which suggests that greater spending on interventions yields more net benefits

continued

TABLE 71 contd *Data extraction tables: economic evaluations*

Study; participants	Interventions, estimated cessation rates; methods	Methods for estimating LYS or QALYs; adjusting factor	Categories of costs considered	Viewpoints; discount rate; dealing with uncertainty	Results	Authors' conclusions; commentary
Fiscella and Franks, 1996,[188] USA Participants: adult smokers (25–69 years old); a base case involving a 45-year-old male smoker	Physician counselling: 4.0% Counselling + NRT patch: 7.9% (based on an OR of 2.06 applied to the spontaneous quit rate) Spontaneous quit rate: 2.5% Relapse rate: 35% (Based on a meta-analysis)	According to mortality data from various sources QALYS/quitter: 1.98 (range 0.69–2.38) (Note: number of quitters after relapse)	Physician time, and retail price of NRT patch	Viewpoints: payer Discount rate: costs not discounted; health benefits, 3% Sensitivity analysis and Monte Carlo simulation	(US $, 1995) Counselling + NRT patch: $7332/quitter (lifetime) Costs/QALYS according to age: 25–44 years, men $4546, women $5522; 45–54 years, men $5011, women $5041; 55–64 years, men $7189, women $5672; 65–69 years, men $10,943, women $6983 (Reference: counselling alone)	Use of NRT patch among men and women in primary care is relatively cost-effective
Oster *et al.*, 1986,[189] USA 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 a meta-analysis)	According to data from the American Cancer Society 25-state Cancer Prevention Study LYS/quitter according to age: 35–44 years, men 1.03, women 0.57; 45–54 years, men 1.09, women 0.64; 55–69 years, men 0.82, women 0.55	Physician time, cost of NRT gum	Viewpoints: payers Discount rate: cost not discounted; health benefits, 5% Sensitivity analysis	(US $, 1984) Advice + NRT gum: $3027/quitter Costs/LYS according to age: 35–44 years, men $4526, women $8421; 45–54 years, men $4140, women $7034; 55–69 years, men $5395, women $8129 (Reference: advice alone)	NRT gum is a cost-effective adjunct to physician's advice against cigarette smoking in a primary care setting
Wasley *et al.*, 1997,[190] USA Participants: a hypothetical group of 400 smokers (> 20 cigarettes/day), aged 35–69 years; a base case involving a 45-year-old male smoker	Physician's advice: 4.5% Advice + NRT patch: 17.6% Spontaneous quit rate: 1% Relapse rate: 35% (Based on a meta-analysis)	Using data and methods in Oster *et al.*, 1986[189] LYS/quitter: see Oster *et al.*, 1986[189]	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 according to age: 35–44 years, men $1902, women $3475; 45–54 years, men $1822, women $3064; 55–69 years, men $2456, women $3686 (Reference: advice alone)	The NRT patch is cost-effective and less costly per year of life saved than other widely accepted medical practices

continued

***TABLE 71* contd** *Data extraction tables: economic evaluations*

Study; participants	Interventions, estimated cessation rates; methods	Methods for estimating LYS or QALYS; adjusting factor	Categories of costs considered	Viewpoints; discount rate; dealing with uncertainty	Results	Authors' conclusions; commentary
Buck *et al.*, 2000,[193] 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% Pre-contemplating smokers: 2% Spontaneous quit rate: 8% (based on control results in trials) (Retrospective data from the programme)	Using number of quitters as the outcome measure	Costs of workshop and training, physician time, patient time and travelling, 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,[194] USA Participants: 5544 patients attending Mayo Clinic Nicotine Dependence Centre (NDC) from April 1988 to December 1992	Mayo Clinic NDC services: non-physician counselling (60 min), plus possible follow-up session, group therapy, NRT, intensive inpatient treatment, etc. NDC services: 22.2% (6 months) Quit rate for those not receiving NDC service: 10.7%, or 7.6%, or 5.5% Relapse rate: 21.8% after 1 year, 12.2% after 2 years, 1.4% after 3–10 years, 0.0% after 10 years (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): 0.80–1.37 (3%); 0.51–0.85 (5%)	Staff costs; supplies, office and equipment costs; NRT (gum or patch)	Viewpoints: payer Discount rate: cost not discounted; health benefits, 0%, 3%, 5% Sensitivity analysis	(US $, 1993) Cost/LYS (discount rate): $2522–4303 (3%); $4041–6828 (5%) (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 healthcare provider. The treatment cost of $6828/net year of life gained is less than many other currently accepted medical interventions (The cost is not an incremental figure, because the authors did not know how much those in the general population who attempt to stop spend on medications or other interventions in producing the 7.6% 1-year quit rate)

continued

TABLE 71 contd *Data extraction tables: economic evaluations*

Study; participants	Interventions, estimated cessation rates; methods	Methods for estimating LYS or QALYS; adjusting factor	Categories of costs considered	Viewpoints; discount rate; dealing with uncertainty	Results	Authors' conclusions; commentary
Cummings *et al.*, 1989,[195] USA 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 four RCTs)	Based on data from American Cancer Society 25-state Cancer Prevention Study	Physician time, patient education material	Viewpoints: 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,[196] USA Participants: 90,005 adult enrolees in seven employers	Insurance coverage (% for behaviour therapy x NRT): quit x usage rate Standard (50 x 100): 38% x 3.5% Reduced (50 x 50): 31% x 2.4% Flipped (100 x 50): 33% x 5.3% Full (100 x 100): 28% x 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 $, 1993–1994) Average cost per quitter: standard coverage, health plan $797, total $928; reduced coverage, health plan $801, total $1127; flipped coverage, health plan $870, total $1036; full coverage, health plan $1171, total $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 co-payment, its effect on the overall prevalence of smoking was greater
Krumholz *et al.*, 1993,[516] USA Participants: smoking patients who became clinically stable after acute myocardial infarction	Nurse-managed smoking-cessation programme after acute myocardial infarction (initial counselling plus telephone follow-up): 71% Usual group: 45% Relapse rate: not available, but incorporated in 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, other instructional material	Viewpoints: 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 programme after acute myocardial infarction is an extremely cost-effective intervention (NRT not considered in this programme)

continued

***TABLE 71* contd** *Data extraction tables: economic evaluations*

Study; participants	Interventions, estimated cessation rates; methods	Methods for estimating LYS or QALYS; adjusting factor	Categories of costs considered	Viewpoints; discount rate; dealing with uncertainty	Results	Authors' conclusions; commentary
Nielsen and Fiore, 2000,[192] USA Participants: from a trial by Jorenby *et al.*, 1999[41]	Placebo 15.6% Bupropion: 30.3% NRT: 16.4% Bupropion + NRT: 35.5% (Data from the trial by Jorenby *et al.*, 1999[41])	Cost–benefit analysis Benefit (money saved)/quitter: $1654 ($0–1654)	Pharmacological therapy (Benefits: data based on the study by McGhan and Smith[522])	Viewpoints: employers Discount rate: not discounted Sensitivity analysis	(US $, 1998) Benefit in the first post-quit year (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,[191] USA Participants: 100,000 health-plan members and 60,000 adult dependants	Bupropion: no counselling; 13.7%; low-level counselling, 15.4%; high-level counselling, 23.0% Bupropion + NRT: no counselling, 18.9%; low-level counselling, 20.6%; high-level counselling, 28.2% NRT patch: no counselling, 7.7%; low-level counselling, 9.4%; high-level counselling, 17.0% No aid: no counselling, 1.3%; low-level counselling, 3.2%; high-level counselling, 7.5% Relapse rate: depending on the year after cessation (Data from Glaxo Wellcome trials by Hurt *et al.*, 1997[52] and Jorenby *et al.*, 1999[41])	Cost–benefit analysis. Health outcomes estimated based on Centers for Disease Control data about smoking-attributable morbidity and mortality No. of cases of COPD avoided/quitter: 0.19 No. of deaths postponed/quitter: 0.02	Cost of smoking-cessation interventions (based on the study by Cromwell *et al.*[187]); short- and long-term medical expenditure; cost of smoking-related diseases; cost of workplace-related measures	Viewpoints: 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 –4.69 in healthcare cost (Reference: without coverage) Benefit/cost ratio: 4.1–4.7	For the managed-care scenarios involving coverage of bupropion, for every dollar spent covering smoking cessation, $4.10 was saved. For the employer scenarios, for every dollar spent covering smoking cessation, $5.04–6.48 was saved (over a 20-year period)

QALYS, quality-adjusted life-years saved

Appendix 11

Forest plots of NRT effectiveness data

All the figures in this appendix were taken directly from the Cochrane Review[26] without changes. Any errors in the weights are due to rounding errors. Most of the studies included in that review are listed in appendix 12.

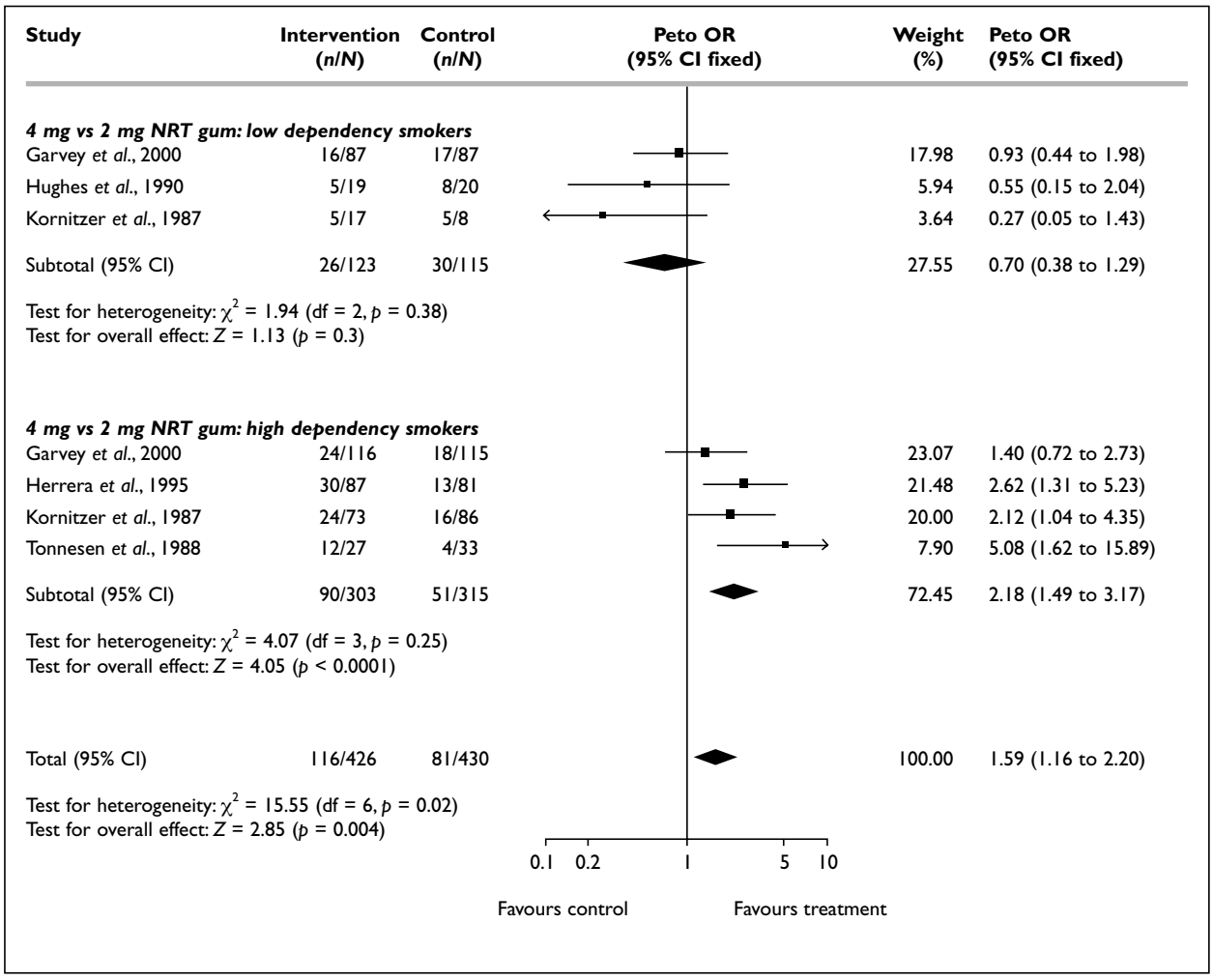


FIGURE 5 *Abstinence from smoking: high-dose versus low-dose NRT gum*

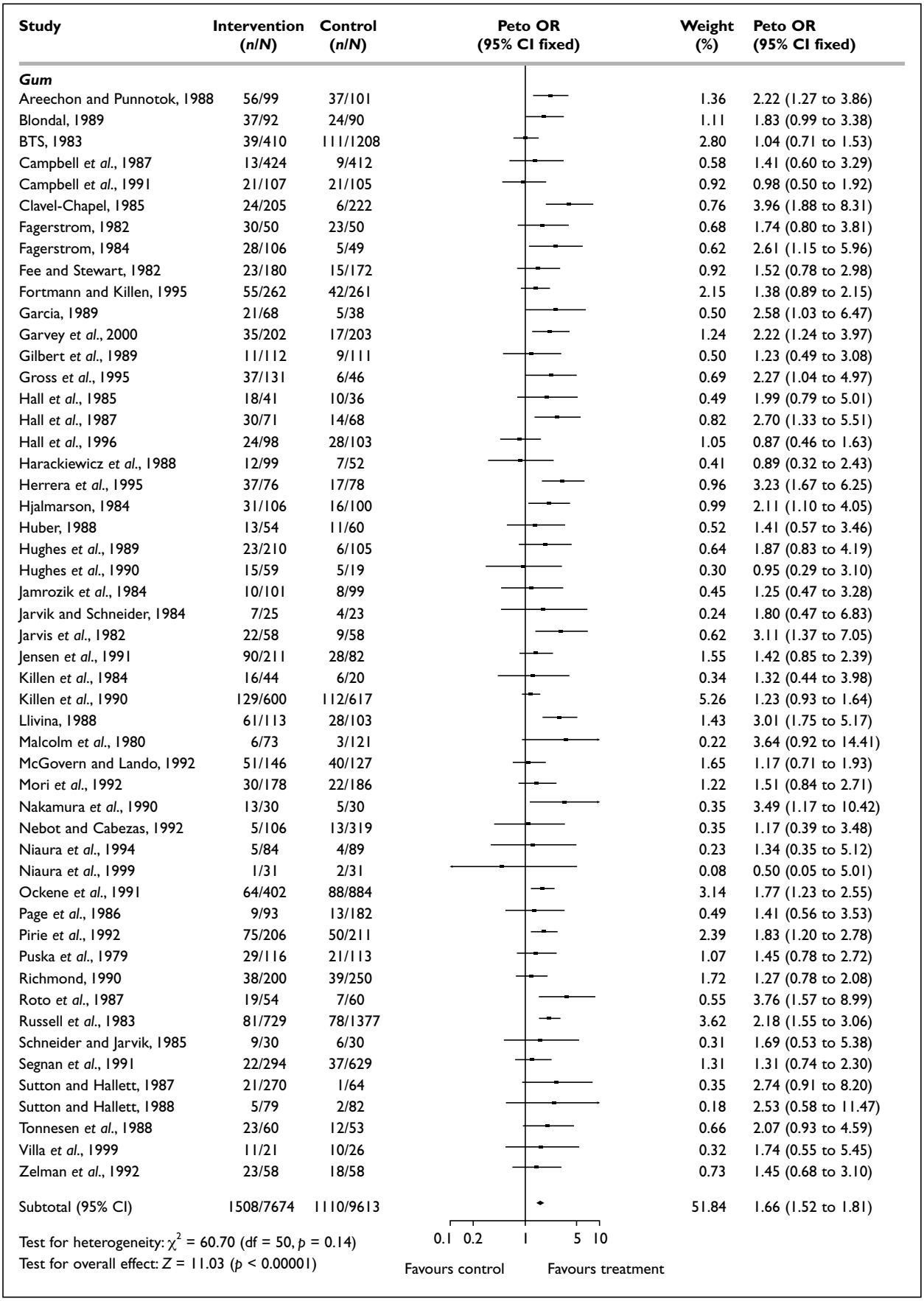


FIGURE 6 *Abstinence from smoking in smokers followed for at least 6 months: NRT versus control (longest duration of follow-up available; published data only)*

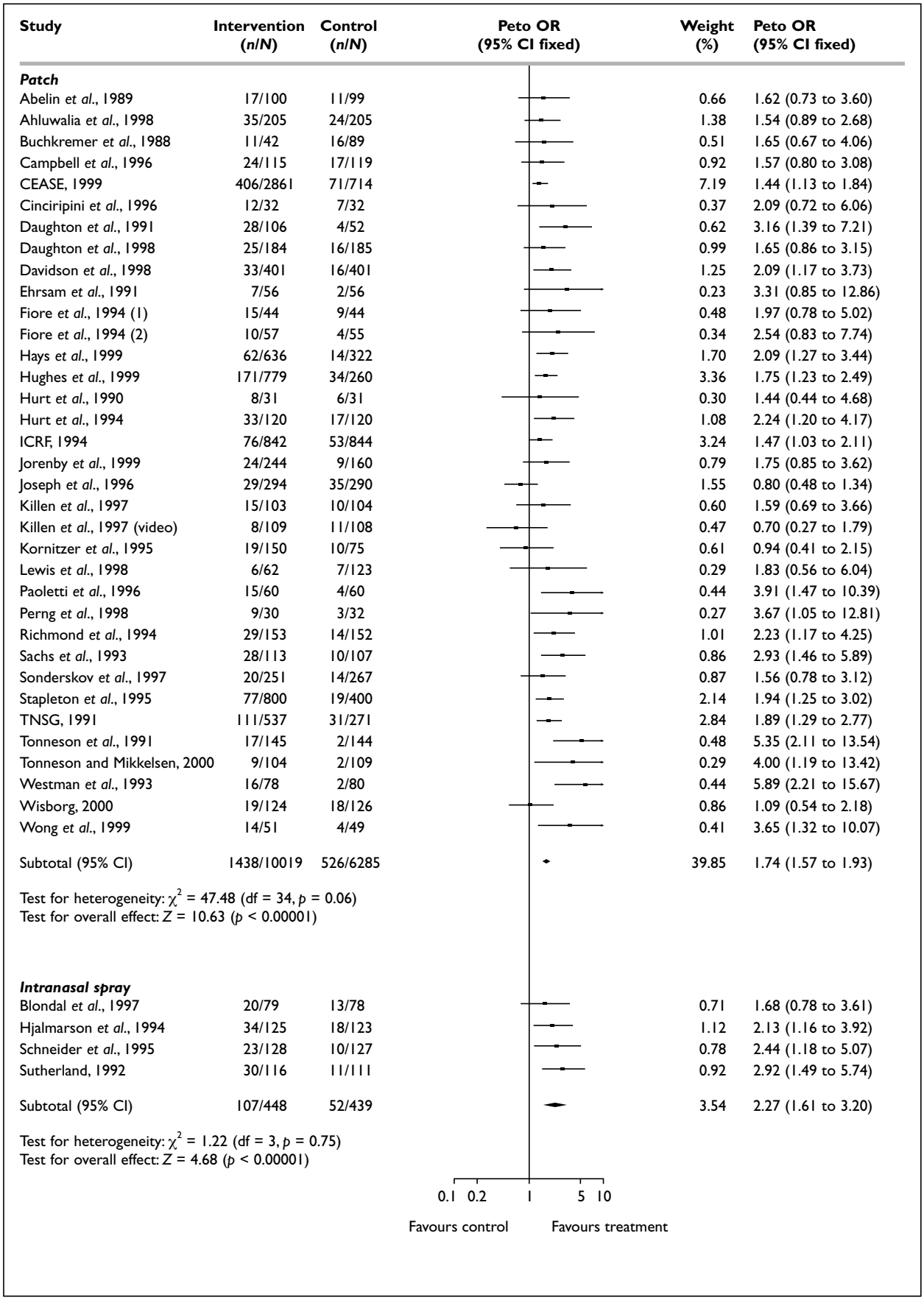
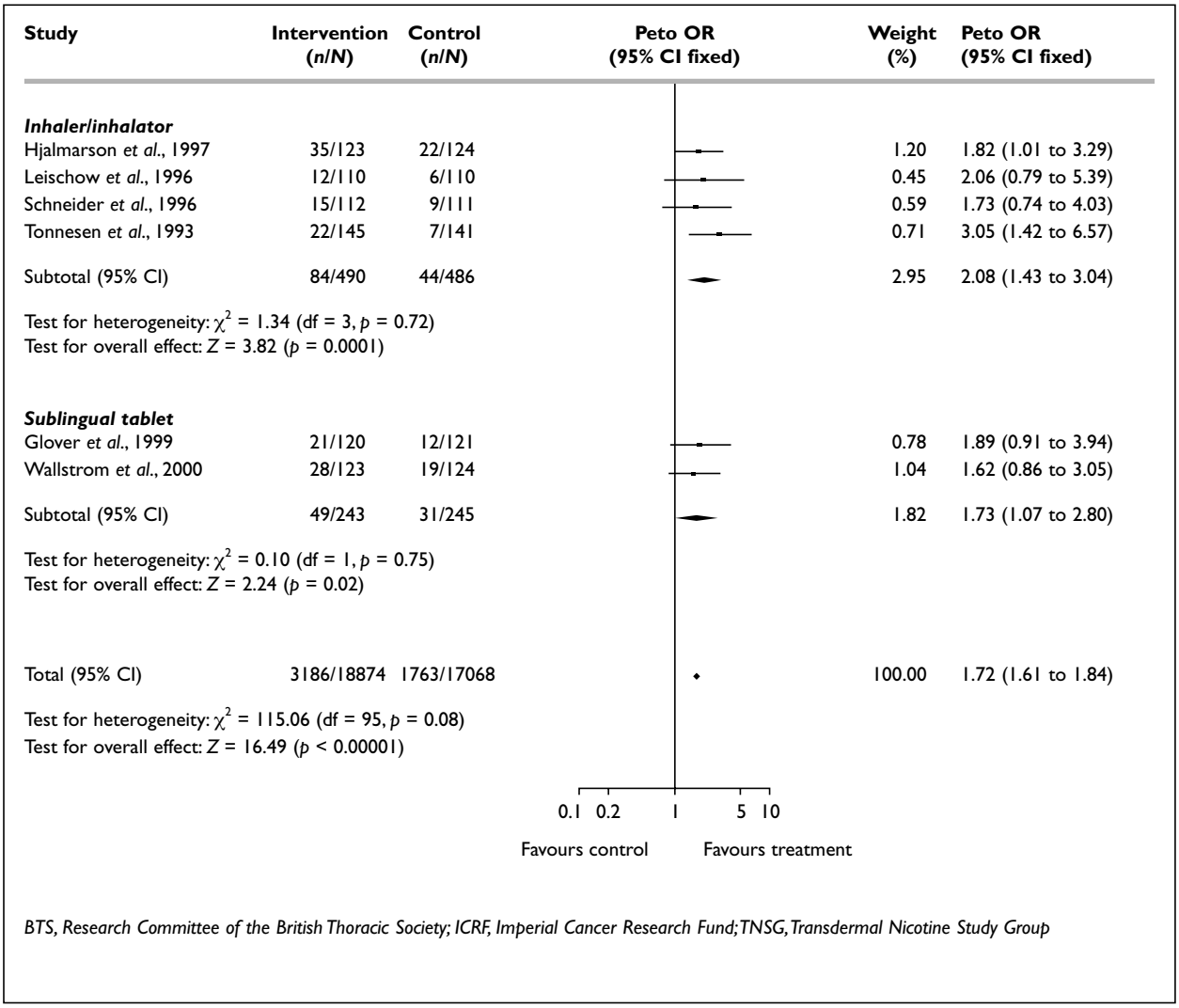


***FIGURE 6* contd** *Abstinence from smoking in smokers followed for at least 6 months: NRT versus control (longest duration of follow-up available; published data only)*



BTS, Research Committee of the British Thoracic Society; ICRF, Imperial Cancer Research Fund; TNSG, Transdermal Nicotine Study Group

***FIGURE 6* contd** *Abstinence from smoking in smokers followed for at least 6 months: NRT versus control (longest duration of follow-up available; published data only)*

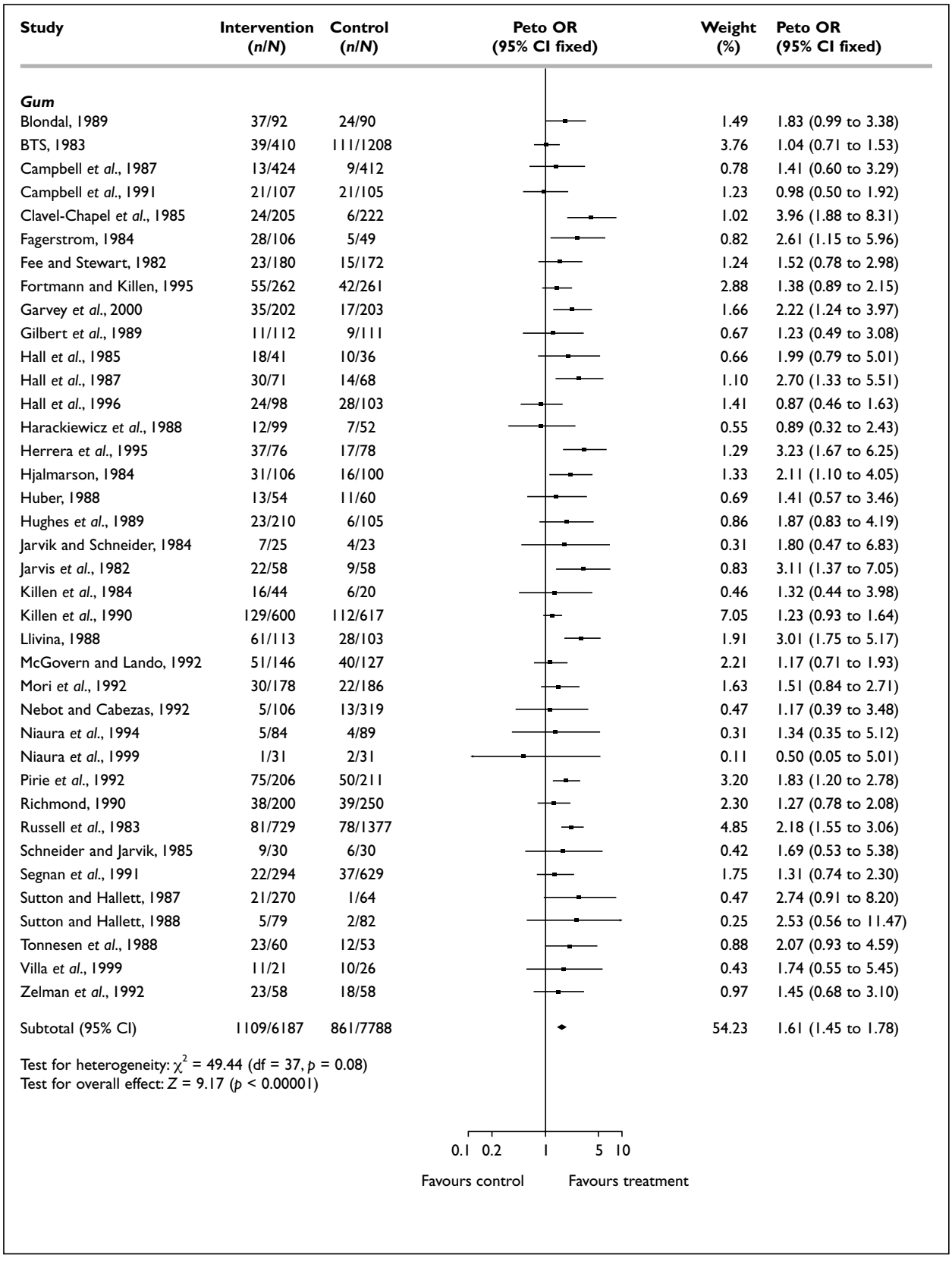


FIGURE 7 *Abstinence from smoking in smokers followed for at least 12 months: NRT versus control (published data only)*

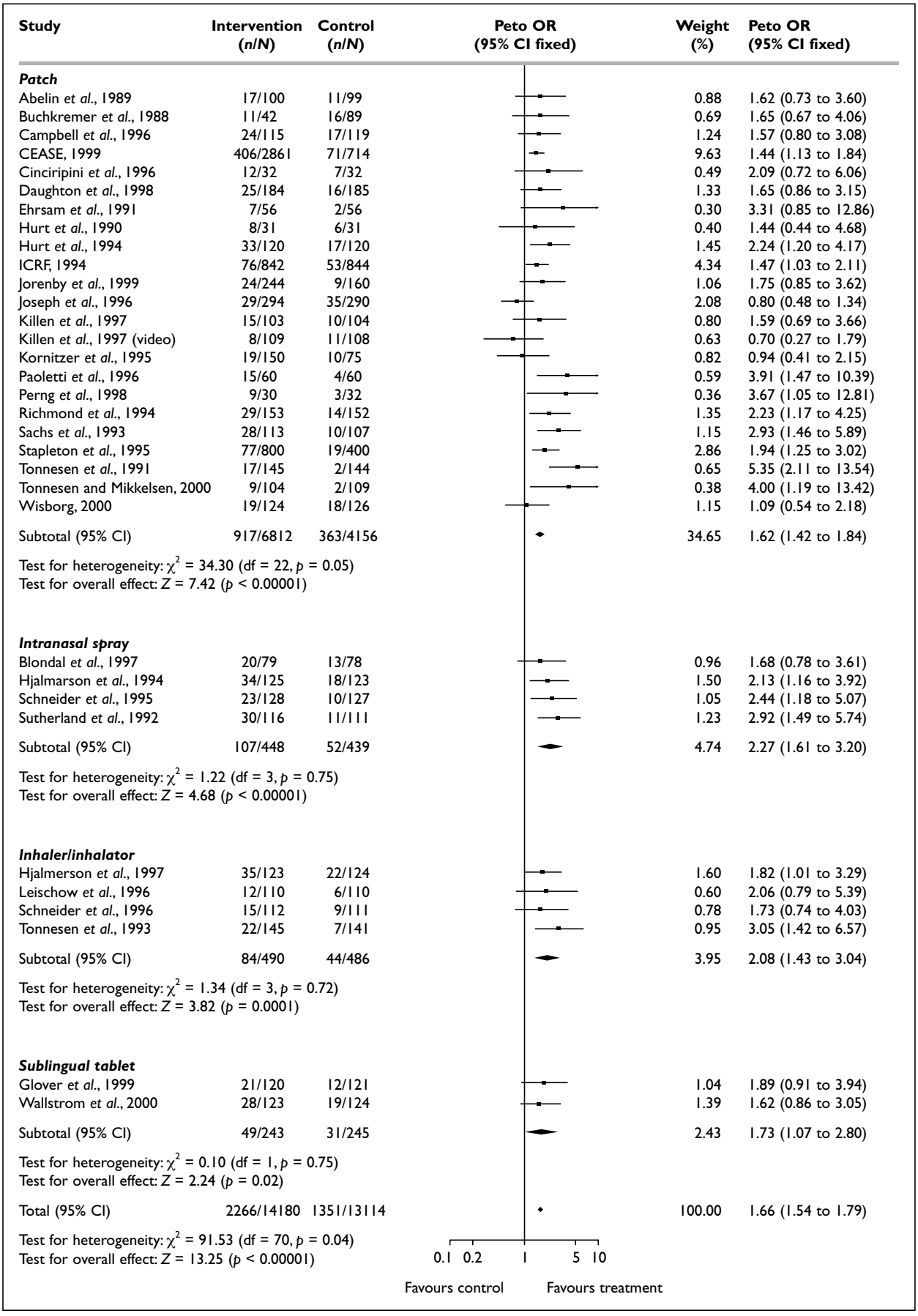


FIGURE 7 contd *Abstinence from smoking in smokers followed for at least 12 months: NRT versus control (published data only)*

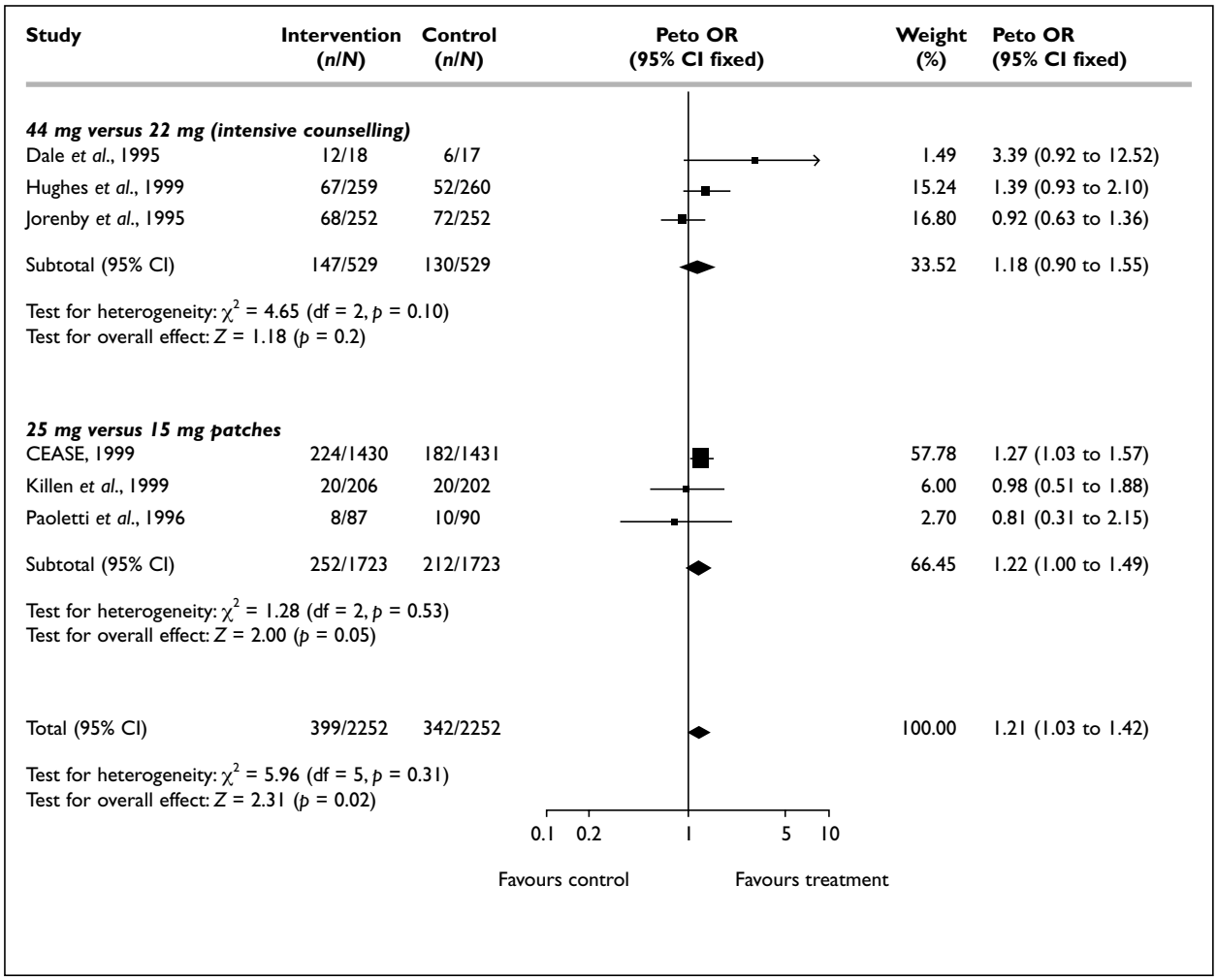


FIGURE 8 *Abstinence from smoking: high-dose versus low-dose NRT patch*

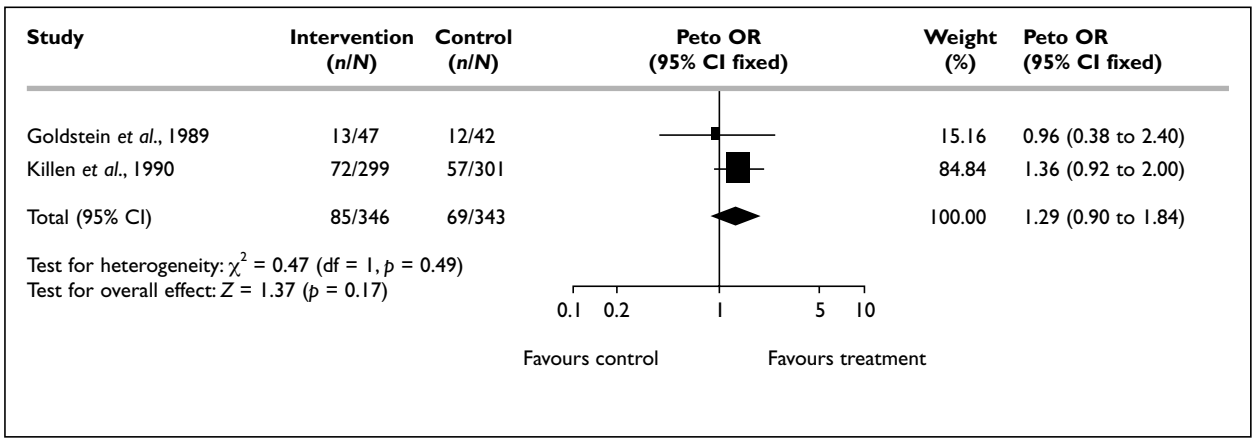


FIGURE 9 *Abstinence from smoking: fixed regimen versus* ad libitum *use of NRT gum*

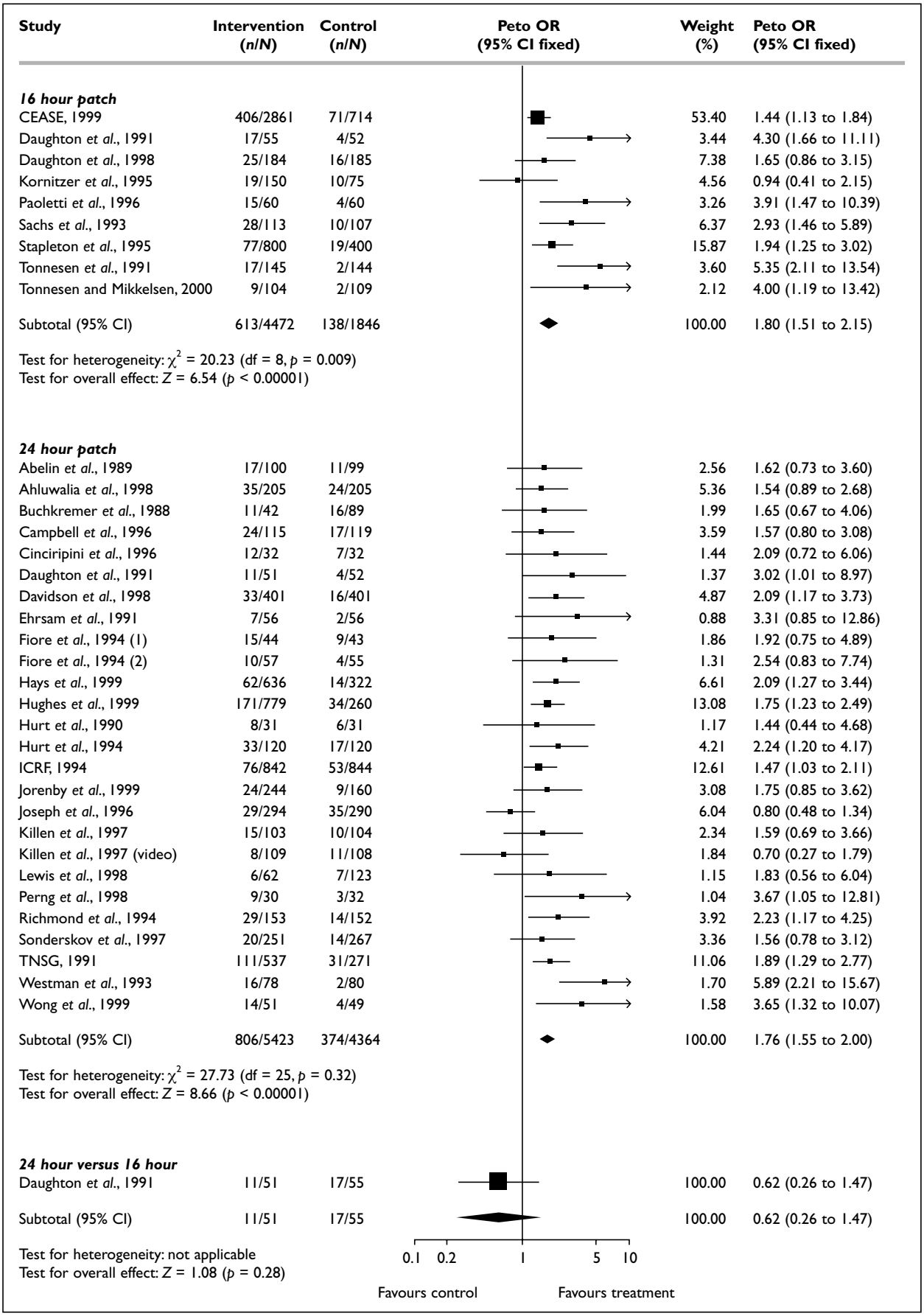


FIGURE 10 *Abstinence from smoking: effect of patch type (24 or 16 hour)*

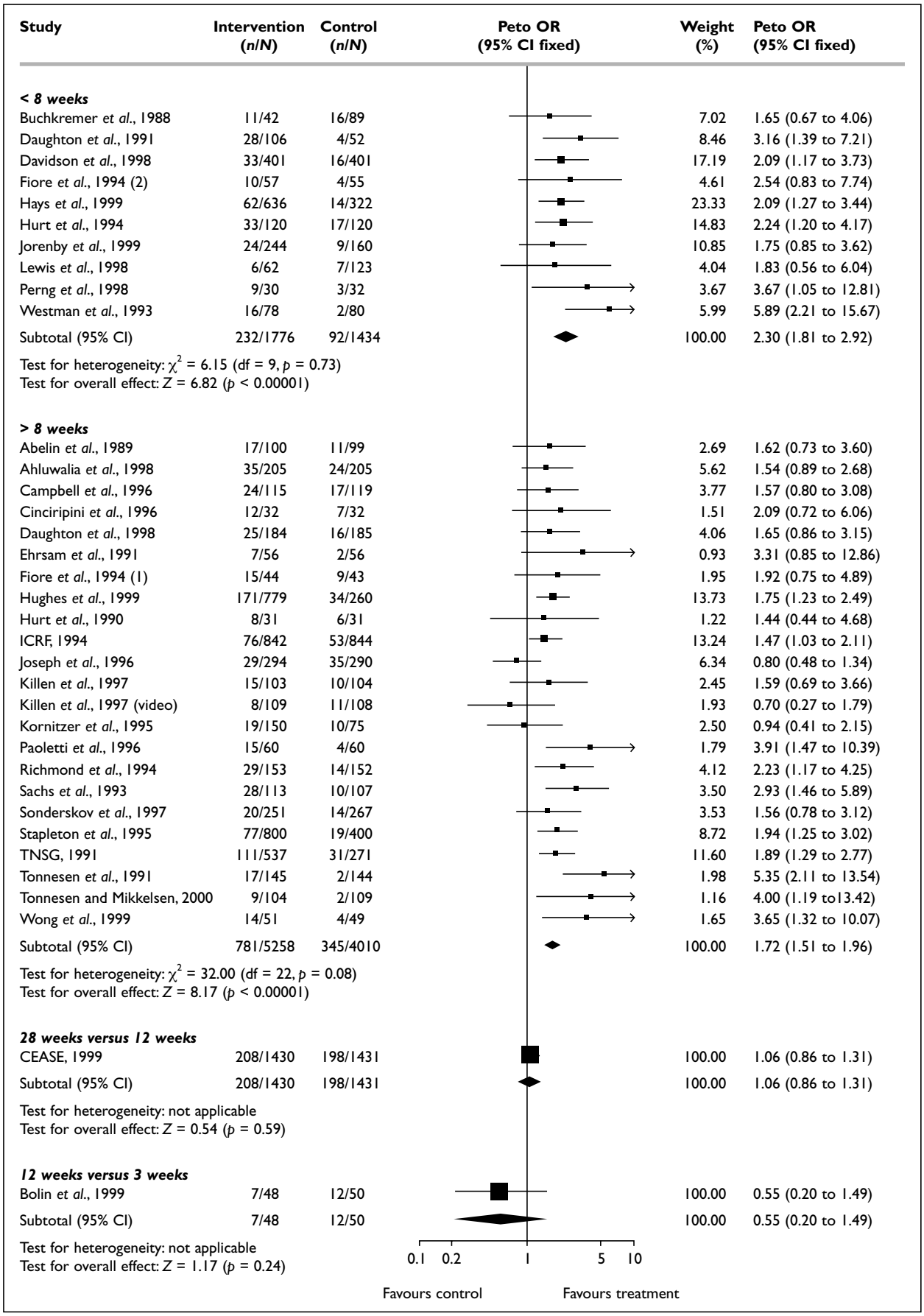


FIGURE 11 *Abstinence from smoking: effect of duration of NRT patch therapy*

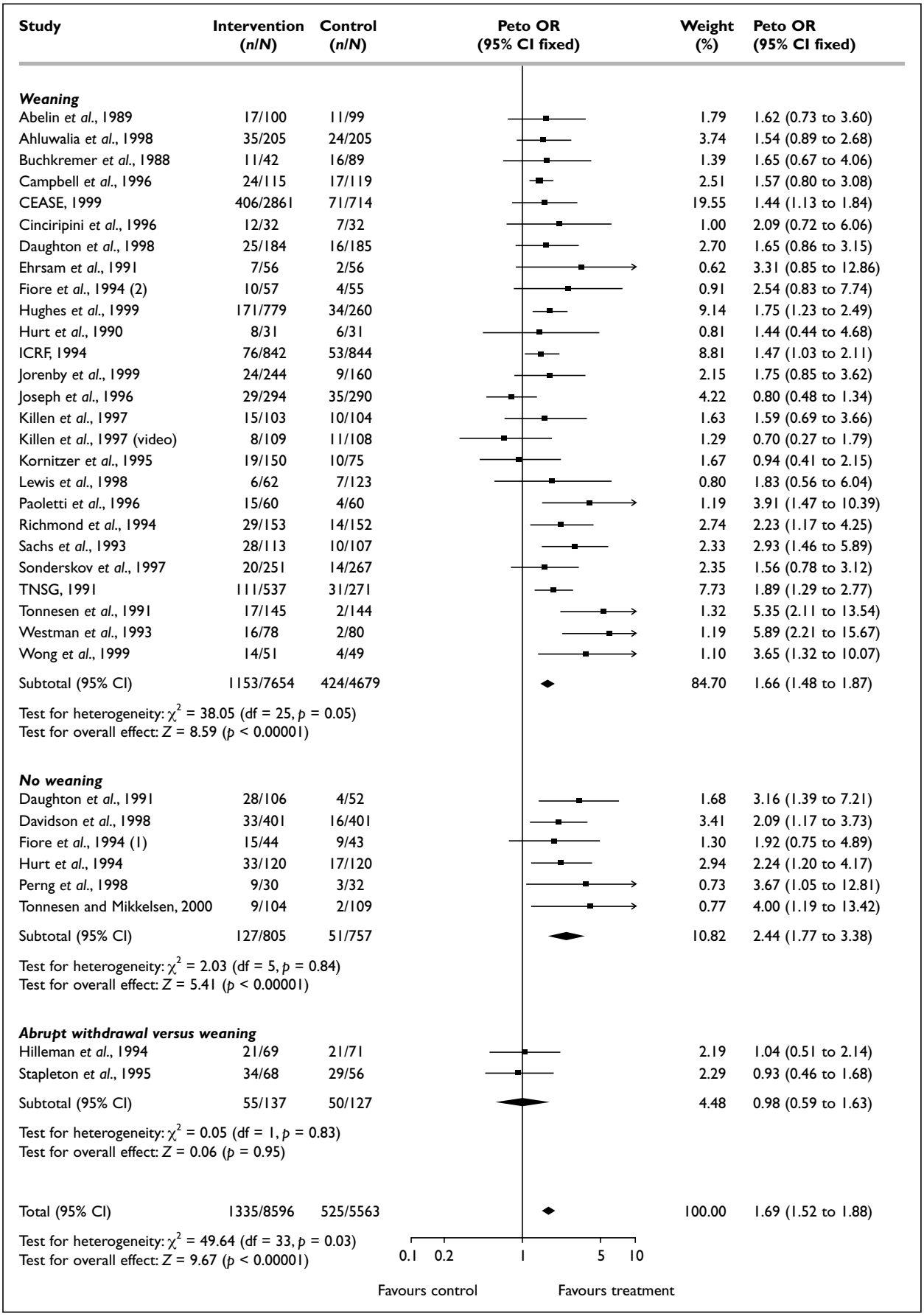


FIGURE 12 *Abstinence from smoking: abrupt versus gradual withdrawal of NRT patch*

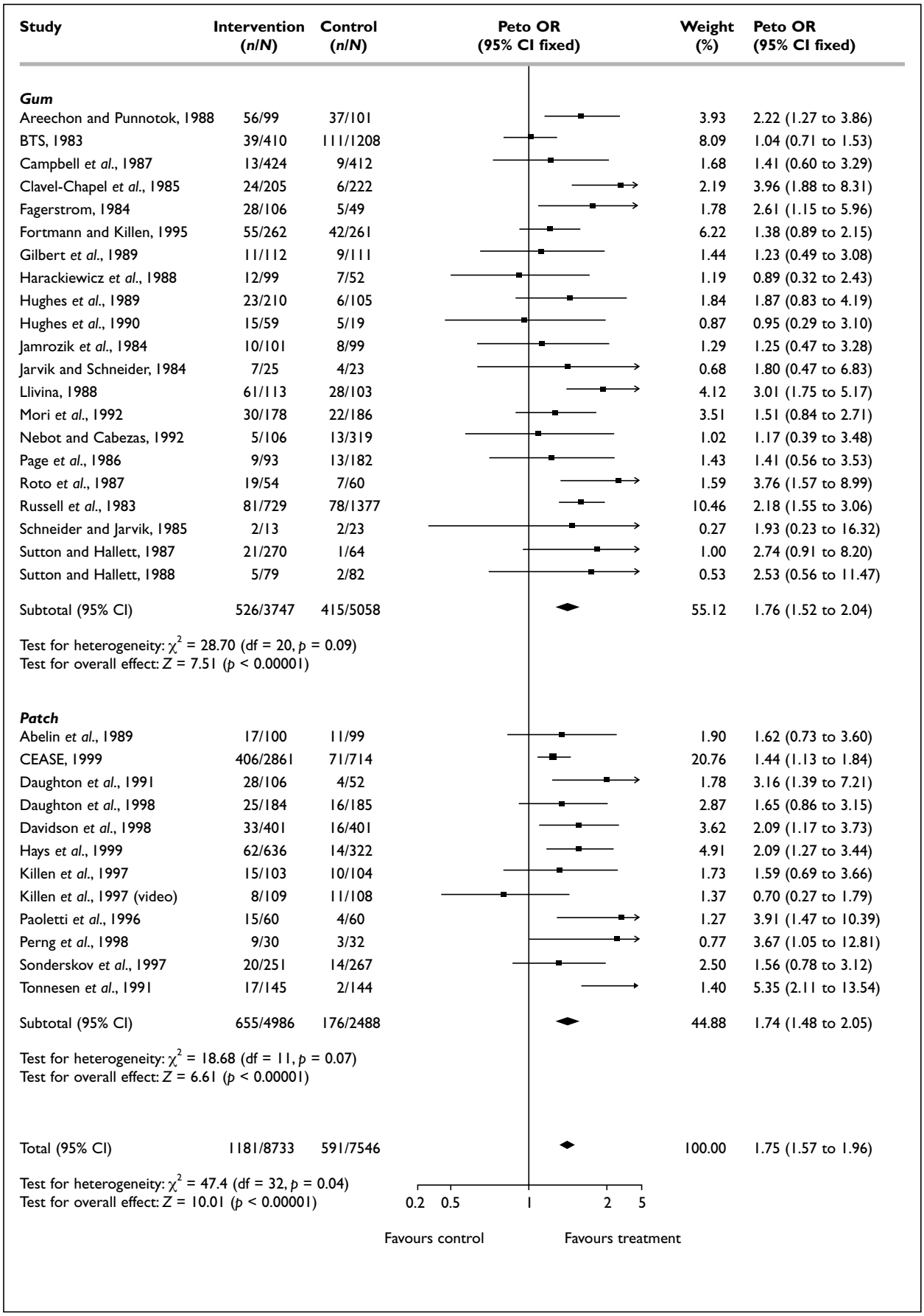


FIGURE 13 *Abstinence from smoking: effect of NRT with low-intensity additional support*

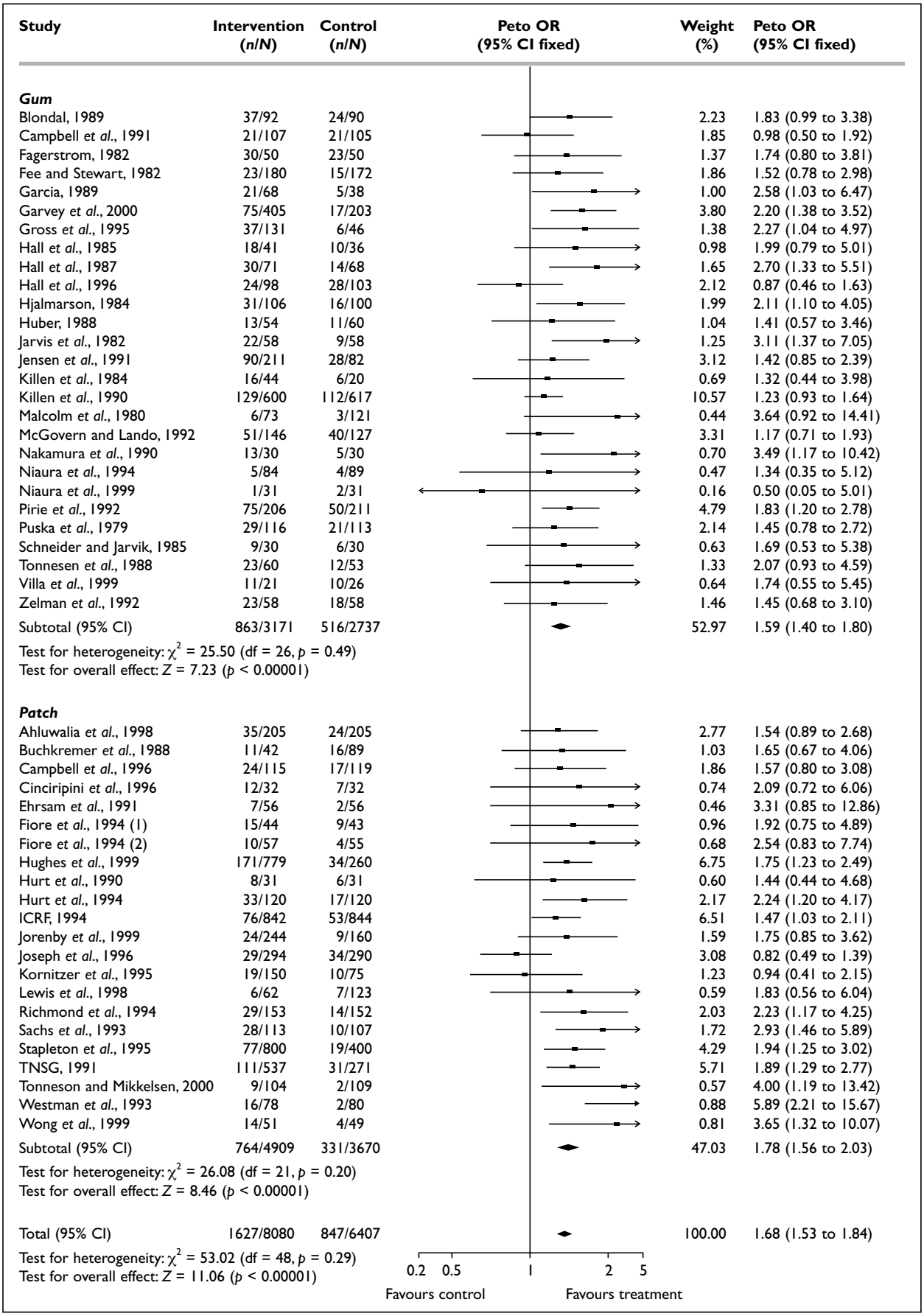


FIGURE 14 *Abstinence from smoking: effect of NRT with high-intensity additional support*

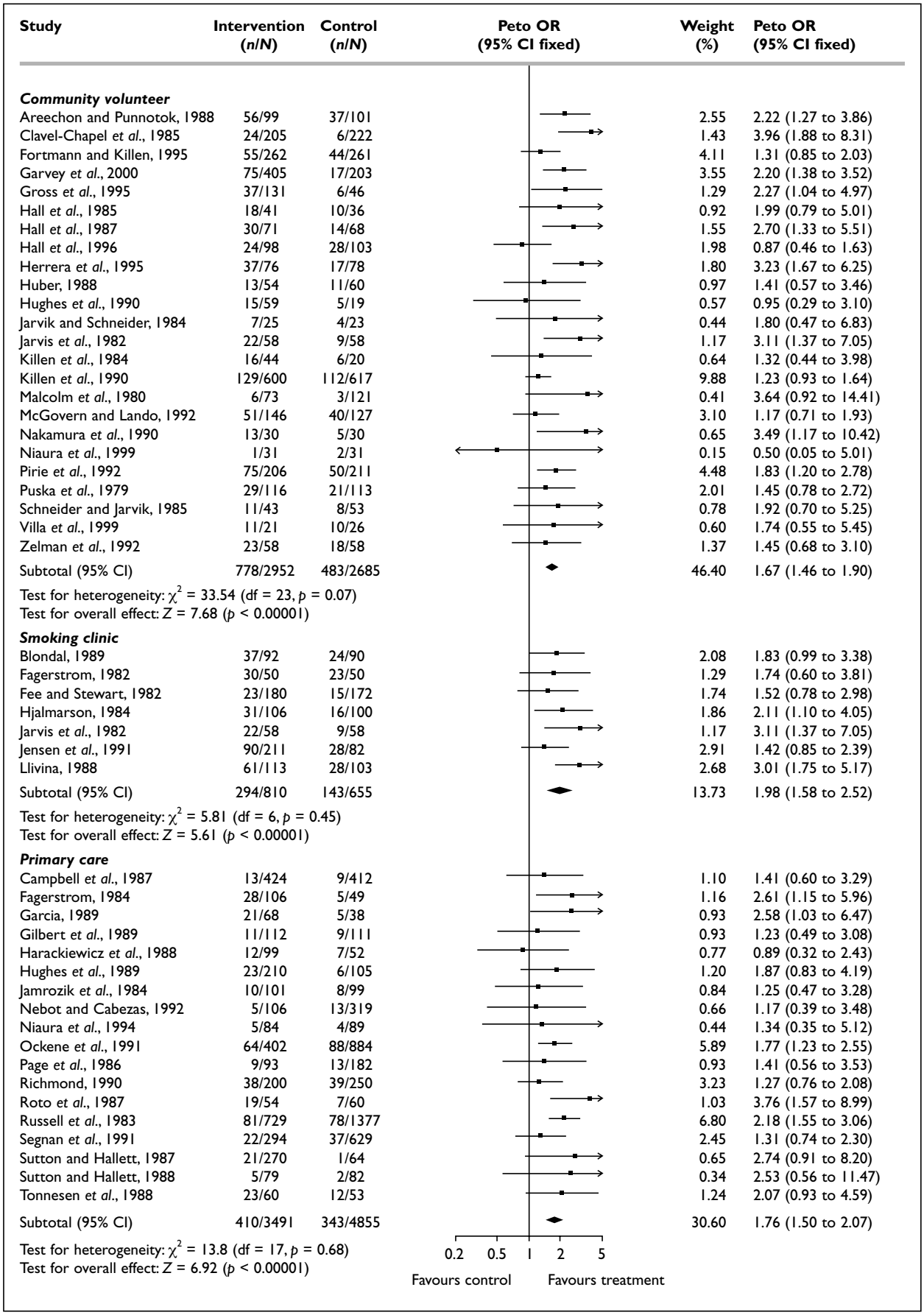


FIGURE 15 *Abstinence from smoking: effect of clinical/recruitment setting, NRT gum*

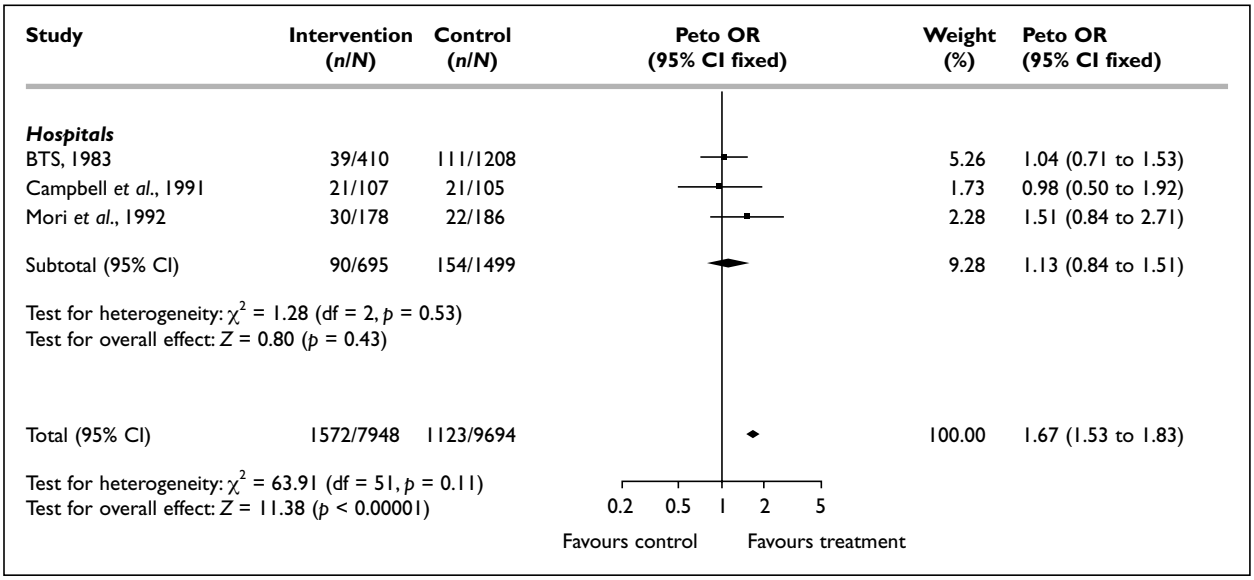


***FIGURE 15* contd** *Abstinence from smoking: effect of clinical/recruitment setting, NRT gum*

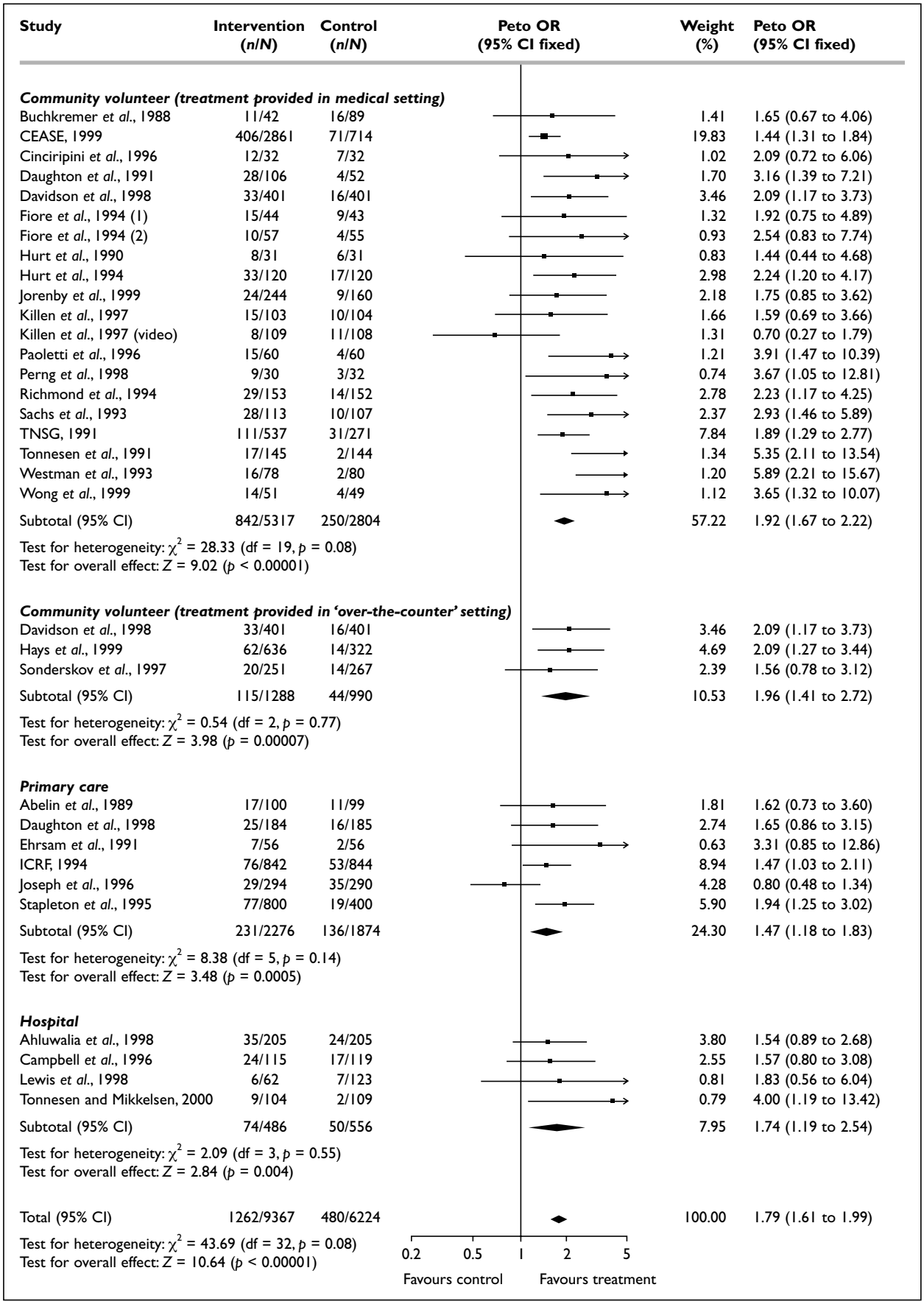


FIGURE 16 *Abstinence from smoking: effect of clinical/recruitment setting, NRT patch*

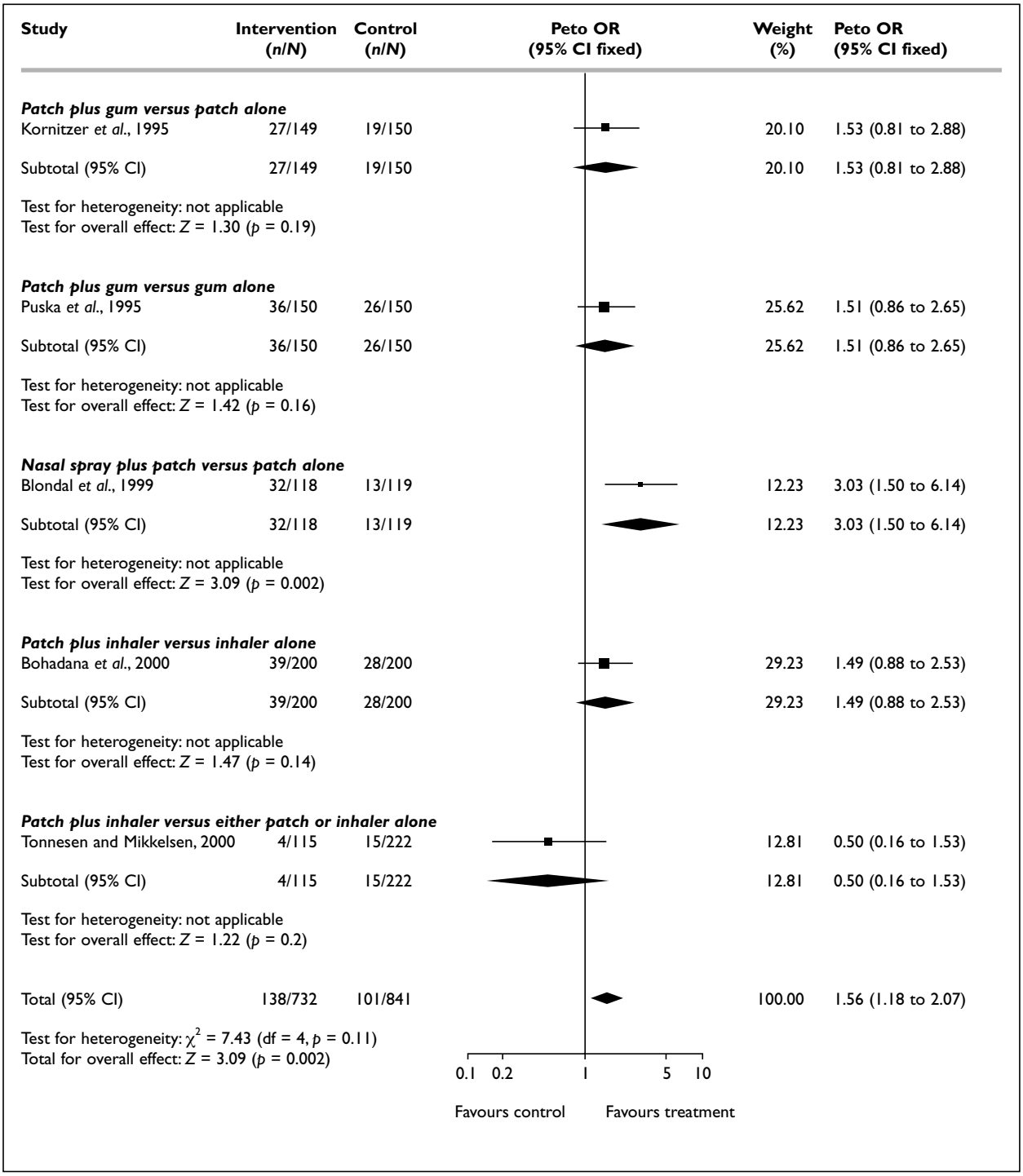


FIGURE 17 *Abstinence from smoking: comparison of various NRT combinations*

Appendix 12

Studies included in systematic reviews

Studies included in the Cochrane Review (NRT for smoking cessation[26])

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.

Abelin T, Buehler A, Muller P, Vesanen K, Imhof PR. Controlled trial of transdermal nicotine patch in tobacco withdrawal. *Lancet* 1989;**1**:7–10.

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. Lewiston, NY: Hogrefe & Huber; 1991. p. 35–46.

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.

Areechon W, Punnotok J. Smoking cessation through the use of nicotine chewing gum: a double-blind trial in Thailand. *Clin Ther* 1988;**10**:183–6.

Blondal T. Controlled trial of nicotine polacrilex gum with supportive measures. *Arch Intern Med* 1989;**149**:1818–21.

Blondal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *Eur Respir J* 1997;**10**:1585–90.

Blondal T, Ludviksdottir D, Gudmundsson L, Olafsdottir I, Gustavsson G, Westin A. Efficacy of nicotine nasal spray added to transdermal nicotine patches in smoking cessation [abstract]. 10th World Conference on Tobacco or Health; 1997 Aug 24–28; Beijing, China. p. 48.

Blondal T, Gudmundsson LJ, Olafsdottir I, Gustavsson G, Westin A. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ* 1999;**318**:285–9.

Bohandana AB, Nilsson F, Martinet Y. Nicotine inhaler and nicotine patch: a combination therapy for smoking cessation [abstract]. *Nicotine Tobacco Res* 1999;**1**:189.

Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 2000; **160**:3128–34.

Bolin LJ, Antonuccio DO, Follette WC, Krumpe P. Transdermal nicotine: the long and the short of it. *Psychol Addict Behav* 1999;**13**:152–6.

Bolliger CT, Zellweger JP, Danielsson T, Van Biljon X, Robidou A, Westin A, *et al.* Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *BMJ* 2000;**321**:329–33.

Buchkremer G, Bents H, Minneker E, Opitz K. [Long-term effects of smoking cessation therapy combining behavior therapy and transdermal nicotine substitution.] *Nervenarzt* 1988;**59**:488–90.

Buchkremer G, Bents H, Horstmann M, Opitz K, Tolle R. Combination of behavioral smoking cessation with transdermal nicotine substitution. *Addict Behav* 1989;**14**:229–38.

Burton S, Campbell IA, Prescott RJ. Nicotine patches versus placebo in 235 hospital patients. 8th World Conference on Tobacco or Health; 1992 30 Mar–3 Apr; Buenos Aires, Argentina. Abstract 191

Campbell IA, Lyons E, Prescott R. Do nicotine chewing-gum and postal encouragement add to doctors' advice. *Practitioner* 1987;**231**:114–17.

Campbell IA, Prescott RJ, Tjeder-Burton SM. Smoking cessation in hospital patients given repeated advice plus nicotine or placebo chewing gum. *Respir Med* 1991;**85**:155–7.

Campbell IA, Prescott RJ, Tjeder-Burton SM. Nicotine patches v placebo in 234 hospital patients. *Thorax* 1992;**45**:835–40.

Campbell IA, Prescott RJ, Tjeder Burton SM. Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study. *Respir Med* 1996;**90**:47–51.

Cinciripini PM, Cinciripini LG, Wallfisch A, Haque W. Behavior therapy and the transdermal nicotine patch: effects on cessation outcome, affect, and coping. *J Consult Clin Psychol* 1996;**64**:314–23.

Clavel F, Benhamou S, Company Huertas A, Flamant R. Helping people to stop smoking: randomised comparison of groups being treated with acupuncture and nicotine gum with control group. *BMJ* 1985;**291**:1538–9.

Dale LC, Hurt RD, Offord KP, Lawson GM, Croghan IT, Schroeder DR. High-dose nicotine patch therapy: percentage of replacement and smoking cessation. *JAMA* 1995;**274**:1353–8.

Dale LC, Schroeder DR, Wolter TD, Croghan IT, Hurt RD, Offord KP. Weight change after smoking cessation using variable doses of transdermal nicotine replacement. *J Gen Intern Med* 1998;**13**:9–15.

Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, *et al.* Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1991;**151**:749–52.

Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, *et al.* Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Monaldi Mal Torace* 1992;**47**:17–29.

Daughton D, Susman J, Sitorius M, Belenky S, Millatmal T, Nowak R, *et al.* Transdermal nicotine therapy and primary care. Importance of counseling, demographic, and participant selection factors on 1-year quit rates. The Nebraska Primary Practice Smoking Cessation Trial Group. *Arch Family Med* 1998;**7**:425–30.

Daughton DM, Fortmann SP, Glover ED, Hatsukami DK, Heatley SA, Lichtenstein E, *et al.* The smoking cessation efficacy of varying doses of nicotine patch delivery systems 4 to 5 years post-quit day. *Prev Med* 1999;**28**:113–18.

Davidson M, Epstein M, Burt R, Schaefer C, Whitworth G, McDonald A. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. *Arch Family Med* 1998;**7**:569–74.

Doherty K, Militello FS, Kinnunen T, Garvey AJ. Nicotine gum dose and weight gain after smoking cessation. *J Consult Clin Psychol* 1996;**64**:799–807.

Ehrsam RE, Buhler A, Muller P, Mauli D, Schumacher PM, Howald H, *et al.* Entwohnung junger Raucher mit Hilfe eines transdermalen Nikotinpflasters. [Weaning of young smokers using a transdermal nicotine patch.] *Schweiz Rundsch Med Prax* 1991;**80**:145–50.

Elan Pharmaceutical Research Corp. NDA 19–983 for approval of PROSTEP; 1992. Study 90–03.

Elan Pharmaceutical Research Corp. NDA 19–983 for approval of PROSTEP; 1992. Study 88–02.

Fagerstrom KO. A comparison of psychological and pharmacological treatment in smoking cessation. *J Behav Med* 1982;**5**:343–51.

Fagerstrom KO. Tolerance. withdrawal and dependence on tobacco and smoking termination. *Int Rev Appl Psychol* 1983;**32**:29–52.

Fagerstrom KO. Effects of nicotine chewing gum and follow-up appointments in physician-based smoking cessation. *Prev Med* 1984;**13**:517–27.

Fee WM, Stewart MJ. A controlled trial of nicotine chewing gum in a smoking withdrawal clinic. *Practitioner* 1982;**226**:148–51.

Fiore MC, Kenford SL, Jorenby DE, Wetter DW, Smith SS, Baker TB. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest* 1994;**105**:524–33.

Fortmann SP, Killen JD. Nicotine gum and self-help behavioral treatment for smoking relapse prevention – results from a trial using population-based recruitment. *J Consult Clin Psychol* 1995;**63**:460–8.

Fortmann SP, Killen JD, Telch MJ, Newman B. Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford Stop Smoking Project. *JAMA* 1988;**260**:1575–80.

Garvey AJ, Kinnunen T, Nordstrom BL, Utman CH, Doherty K, Rosner B, *et al.* Effects of nicotine gum dose by level of nicotine dependence. *Nicotine Tobacco Res* 2000;**2**:53–63.

Gilbert JR, Wilson DM, Best JA, Taylor DW, Lindsay EA, Singer J, *et al.* Smoking cessation in primary care. A randomized controlled trial of nicotine-bearing chewing gum. *J Family Pract* 1989;**28**:49–55.

Glover ED, Glover PN, Franzon M, Sullivan R, Sullivan P, Howell R, *et al.* A nicotine sublingual tablet for smoking cessation: 6-month data. 10th World Conference on Tobacco or Health; 1997 Aug 24–28; Beijing, China. Abstract.

Glover E, Glover P, Franzon M, Sullivan R, Cerullo C. Safety and efficacy of a nicotine sublingual tablet for smoking cessation. Smoke Free 21st Century. 2nd European Conference on Tobacco or Health; 1999 Feb 23–27; Las Palmas de Gran Canaria. Abstract.

Goldstein MG, Niaura R, Follick MJ, Abrams DB. Effects of behavioral skills training and schedule of nicotine gum administration on smoking cessation. *Am J Psychiatry* 1989;**146**:56–60.

Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ* 1995;**311**:363–6.

Gross J, Johnson J, Sigler L, Stitzer ML. Dose effects of nicotine gum. *Addict Behav* 1995;**20**:371–81.

Hall SM, Tunstall C, Rugg D, Jones R, Benowitz N. Nicotine gum and behavioral treatment in smoking cessation. *J Consult Clin Psychol* 1985;**53**:256–8.

Hall SM, Tunstall CD, Ginsberg D, Benowitz NL, Jones RT. Nicotine gum and behavioral treatment: a placebo controlled trial. *J Consult Clin Psychol* 1987; **55**:603–5.

Hall SM, Munoz RF, Reus VI, Sees KL, Duncan C, Humfleet GL, *et al.* Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. *J Consult Clin Psychol* 1996;**64**:1003–9.

Harackiewicz JM, Blair LW, Sansone C, Epstein JA, Stuchell RN. Nicotine gum and self-help manuals in smoking cessation: an evaluation in a medical context. *Addict Behav* 1988;**13**:319–30.

Hays JT, Croghan GA, Offord KP, Wolter TD, Nides MA, Davidson M. Over-the-counter (OTC) transdermal nicotine patch therapy [abstract]. *J Addict Dis* 1997;**16**:136.

Hays JT, Croghan IT, Schroeder DR, Offord KP, Hurt RD, Wolter TD, *et al.* Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled, and open label trials. *Am J Publ Health* 1999;**89**:1701–7.

Hays JT, Croghan IT, Offord KP, Hurt RD, Schroeder DR, Wolter TD, *et al.* Over the counter 22 mg nicotine patch therapy for smoking cessation: results from randomized double-blind placebo-controlled and open label trials. Society for Research on Nicotine and Tobacco 5th Annual Meeting; 1999 Mar 5–7; San Diego, CA, USA.

Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerstrom KO. Nicotine gum, 2 and 4 mg, for nicotine dependence: a double-blind placebo-controlled trial within a behavior-modification support program. *Chest* 1995;**108**:447–51.

Hilleman DE, Mohiuddin SM, Delcore MG. Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. *J Clin Pharmacol* 1994;**34**:222–4.

Hjalmarson AI. Effect of nicotine chewing gum in smoking cessation. A randomized, placebo-controlled, double-blind study. *JAMA* 1984;**252**:2835–8.

Hjalmarson A, Franzon M, Westin A, Wiklund O. Effect of nicotine nasal spray on smoking cessation: a randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1994;**154**:2567–72.

Hjalmarson A, Nilsson F, Sjostrom L, Wiklund O. The nicotine inhaler in smoking cessation. *Arch Intern Med* 1997;**157**:1721–8.

Huber D. Combined and separate treatment effects of nicotine chewing gum and self-control method. *Pharmacopsychiatry* 1988;**21**:461–2.

Hughes JR, Gust SW, Keenan RM, Fenwick JW, Healey ML. Nicotine vs placebo gum in general medical practice. *JAMA* 1989;**261**:1300–5.

Hughes JR, Gust SW, Keenan RM, Fenwick JW. Effect of dose on nicotine's reinforcing, withdrawal-suppression and self-reported effects. *J Pharmacol Exp Ther* 1990;**252**:1175–83.

Hughes JR, Lesmes GR, Hatsukami DK, Richmond RL, Lichtenstein E, Jorenby DE, *et al.* Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tobacco Res* 1999;**1**:169–74.

Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine-replacement therapy with use of a transdermal nicotine patch – a randomized double-blind placebo-controlled trial. *Mayo Clin Proc* 1990;**65**:1529–37.

Hurt RD, Dale LC, Fredrickson PA, Caldwell CC, Lee GA, Offord KP, *et al.* Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: one-year outcome and percentage of nicotine replacement. *JAMA* 1994;**271**:595–600.

Imperial Cancer Research Fund General Practice Research Group. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomized trial in general practice. *BMJ* 1993;**306**:1304–8.

Imperial Cancer Research Fund General Practice Research Group. Randomised trial of nicotine patches in general practice: results at one year. *BMJ* 1994;**308**:1476–7.

Jamrozik K, Fowler G, Vessey M, Wald N. Placebo controlled trial of nicotine chewing gum in general practice. *BMJ* 1984;**289**:794–7.

Jarvik ME, Schneider NG. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *Am J Psychiatry* 1984;**141**:790–1.

Jarvis MJ, Raw M, Russell MA, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. *Br Med J Clin Res Ed* 1982;**285**:537–40.

Jensen EJ, Schmidt E, Pedersen B, Dahl R. The effect of nicotine, silver acetate, and placebo chewing gum on the cessation of smoking. The influence of smoking type and nicotine dependence. *Int J Addict* 1991;**26**:1223–31.

Jorenby DE, Smith SS, Fiore MC, Hurt RD, Offord KP, Croghan IT, *et al.* Varying nicotine patch dose and type of smoking cessation counseling. *JAMA* 1995;**274**:1347–52.

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New Engl J Med* 1999;**340**:685–91.

Joseph AM, Antonnucio DO. Lack of efficacy of transdermal nicotine in smoking cessation (3). *New Engl J Med* 1999;**341**:1157–8.

Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, *et al.* The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *New Engl J Med* 1996;**335**:1792–8.

Kenford SL, Fiore MC, Jorenby DE, Smith SS. Predicting smoking cessation: who will quit with and without the nicotine patch. *J Am Med Assoc* 1994;**271**:589–94.

Killen JD, Maccoby N, Taylor CB. Nicotine gum and self-regulation training in smoking relapse prevention. *Behav Ther* 1984;**15**:234–48.

Killen JD, Fortmann SP, Newman B, Varady A. Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. *J Consult Clin Psychol* 1990;**58**:85–92.

Killen JD, Fortmann SP, Davis L, Varady A. Nicotine patch and self-help video for cigarette smoking cessation. *J Consult Clin Psychol* 1997;**65**:663–72.

Killen JD, Fortmann SP, Davis L, Strausberg L, Varady A. Do heavy smokers benefit from higher dose nicotine patch therapy? *Exp Clin Psychopharmacol* 1999;**7**:226–33.

Kornitzer M, Kittel F, Dramaix M, Bourdoux P. A double blind study of 2 mg versus 4 mg nicotine-gum in an industrial setting. *J Psychosom Res* 1987;**31**:171–6.

Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med* 1995;**24**:41–7.

Leischow SJ, Nilsson F, Franzon M, Hill A, Otte P, Merikle EP. Efficacy of the nicotine inhaler as an adjunct to smoking cessation. *Am J Health Behav* 1996;**20**:364–71.

Leischow SJ, Muramoto ML, Cook GN, Merikle EP, Castellini SM, Otte PS. OTC nicotine patch: effectiveness alone and with brief physician intervention. *Am J Health Behav* 1999;**23**:61–9.

Lewis SF, Piasecki TM, Fiore MC, Anderson JE, Baker TB. Transdermal nicotine replacement for hospitalized patients: a randomized clinical trial. *Prev Med* 1998;**27**:296–303.

Malcolm RE, Sillett RW, Turner JA, Ball KP. The use of nicotine chewing gum as an aid to stopping smoking. *Psychopharmacol Ser* 1980;**70**:295–6.

Marshall A, Raw M. Nicotine chewing gum in general practice: effect of follow up appointments. *BMJ* 1985; **290**:1397–8.

McGovern PG, Lando HA. An assessment of nicotine gum as an adjunct to freedom from smoking cessation clinics. *Addict Behav* 1992;**17**:137–47.

Mikkelsen KL, Tonnesen R, Norregaard J. Three-year outcome of two- and tree-year sustained abstainers from a smoking cessation study with nicotine patches. *J Smoking-Related Dis* 1994;**5**:95–100.

Mori T, Shimao T, Yulchiro G, Namiki M, Hyachi T. A clinical trial of nicotine chewing gum for smoking cessation. 8th World Conference on Tobacco or Health; 1992 Mar 30–Apr 3; Buenos Aires, Argentina; 1992. Abstract 428.

Nakamura M, Saito J, Oshima A, Miyamoto M, Matushita A, Endo S. Effect of nicotine chewing gum in smoking cessation classes. In: Durston B, Jamrozik K, editors. The Global War. Proceedings of the 7th World Conference on Tobacco and Health; 1990 Apr 1–5; Perth, Western Australia. Perth: Health Department of Western Australia; 1990.

Nebot M, Cabezas C. Does nurse counseling or offer of nicotine gum improve the effectiveness of physician smoking-cessation advice? *Family Practice Res J* 1992; **12**:263–70.

Niaura R, Abrams DB, Shadel WG, Rohsenow DJ, Monti PM, Sirota AD. Cue exposure treatment for smoking relapse prevention: a controlled clinical trial. *Addiction* 1999;**94**:685–96.

Niaura R, Goldstein MG, Abrams DB. Matching high and low-dependence smokers to self-help treatment with or without nicotine replacement. *Prev Med* 1994;**23**:70–7.

Nordstrom BL, Kinnunen T, Utman CH, Garvey AJ. Long-term effects of nicotine gum on weight gain after smoking cessation. *Nicotine Tobacco Res* 1999;**1**:259–68.

Norregaard J, Tonnesen P, Petersen L. Predictors and reasons for relapse in smoking cessation with nicotine and placebo patches. *Prev Med* 1993;**22**:261–71.

Ockene JK, Kristeller J, Goldberg R, Amick TL, Pekow PS, Hosmer D, *et al.* Increasing the efficacy of physician-delivered smoking interventions: a randomized clinical trial. *J Gen Intern Med* 1991;**6**:1–8.

Ockene JK, Kristeller J, Pbert L, Hebert JR, Luippold R, Goldberg RJ, *et al.* The physician-delivered smoking intervention project: can short-term interventions produce long-term effects for a general outpatient population? *Health Psychol* 1994;**13**:278–81.

Page AR, Walters DJ, Schlegel RP, Best JA. Smoking cessation in family practice: the effects of advice and nicotine chewing gum prescription. *Addict Behav* 1986;**11**:443–6.

Paoletti P, Fornai E, Maggiorelli F, Puntoni R, Viegi G, Carrozzi L, *et al.* Importance of baseline cotinine plasma values in smoking cessation: results from a double blind study with nicotine patch. *Eur Respir J* 1996;**9**:643–51.

Perng RP, Hsieh WC, Chen YM, Lu CC, Chiang SJ. Randomized, double-blind, placebo-controlled study of transdermal nicotine patch for smoking cessation. *J Formos Med Assoc* 1998;**97**:547–51.

Perng RP, Hsieh WC, Chen YM, Lu CC, Chiang SJ. Randomized, double-blind, placebo-controlled study of transdermal nicotine patch for smoking cessation. *Am J Resp Crit Care Med* 1999;**159**:A735.

Pharmacia & Upjohn. Nicorette nicotine microtab monograph. Chester: Adis International; 1998.

Pirie PL, McBride CM, Hellerstedt WL, Jeffery RW, Hatsukami DK, Allen S, *et al.* Smoking cessation in women concerned about weight. *Am J Public Health* 1992;**82**:1238–43.

Puska P, Bjorkqvist S, Koskela K. Nicotine-containing chewing gum in smoking cessation: a double blind trial with half year follow-up. *Addict Behav* 1979;**4**:141–6.

Puska P, Korhonen HJ, Vartiainen E, Urjanheimo EL, Gustavsson G, Westin A. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. *Tobacco Control* 1995;**4**:231–5.

Quilez Garcia C, Hernando Arizaleta L, Rubio Diaz A, Granero Fernandez EJ, Vila Coll MA, Estruch Riba JSO. Estudio doble ciego de la eficacia del chicle de nicotina en la deshabituacion tabaquica dentro del ambito de la atencion primaria. [Double-blind study of the efficacy of nicotine chewing gum for smoking cessation in the primary care setting.] *Aten Primaria* 1989;**6**:719–26.

Quilez Garcia C, Hernando Arizaleta L, Rubio Diaz A, Estruch Riba J, Fornes Ramis MV. Tratamiento del tabaquismo, con chicle de nicotina, en atencion primaria. Estudio a doble ciego. *Rev Clin Esp* 1993;**192**:157–61.

Research Committee of the British Thoracic Society. Comparison of four methods of smoking withdrawal in patients with smoking related diseases. Report by a subcommittee of the Research Committee of the British Thoracic Society. *BMJ* 1983;**286**:595–7.

Richmond R, Heather N. General practitioner interventions for smoking cessation: past results and future prospects. *Behav Change* 1990;**7**:110–19.

Richmond RL, Makinson RJ, Giugni AA, Webster IW. General practitioner smoking interventions in Australia: results of studies over the past ten years. In: Durston B, Jamrozik K, editors. The Global War. Proceedings of the 7th World Conference on Tobacco and Health. 1990 Apr 1–5; Perth, Western Australia. Perth: Health Department of Western Australia; 1990. p. 657–60.

Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. *Med J Aust* 1994;**161**:130–5.

Richmond RL, Kehoe L, Neto ACD, de Almeida Neto A. Effectiveness of a 24-hour transdermal nicotine patch in conjunction with a cognitive behavioural programme: one year outcome. *Addiction* 1997;**92**:27–31.

Roto P, Ojala A, Sundman K, Jokinen K, Peltomakl R. Nicotine gum and withdrawal from smoking. *Suomen Laakarllehtl* 1987;**36**:3445–8.

Russell MA, Merriman R, Stapleton J, Taylor W. Effect of nicotine chewing gum as an adjunct to general practitioner's advice against smoking. *Br Med J Clin Res Ed* 1983;**287**:1782–5.

Russell MAH, Stapleton JA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, *et al.* Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ* 1993; **306**:1308–12.

Sachs DPL, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med* 1993;**153**:1881–90.

Salvador Llivina T, Marin Tuya D, Gonzalez Quintana J, Iniesta Torres C, Castellvi Barrera E, Muriana Saez C, *et al.* [Smoking cessation: effectiveness of nicotine containing chewing gum. A double-blind trial.] *Med Clin Barc* 1988;**90**:646–50.

Schneider NG, Jarvik ME. Nicotine gum vs placebo gum: comparisons of withdrawal symptoms and success rates. *Nida Res Monogr Ser* 1985;**53**:83–101.

Schneider NG, Jarvik ME, Forsythe AB, Read LL, Elliott ML, Schweiger A. Nicotine gum in smoking cessation: a placebo-controlled. double-blind trial. *Addict Behav* 1983;**8**:253–61.

Schneider NG, Olmstead R, Mody FV, Doan K, Franzon M, Jarvik ME, *et al.* Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. *Addiction* 1995;**90**:1671–82.

Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. *Addiction* 1996;**91**:1293–306.

Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial [abstract]. *Addiction* 1997;**92**:630.

Segnan N, Ponti A, Battista RN, Senore C, Rosso S, Shapiro SH, *et al.* A randomized trial of smoking cessation interventions in general practice in Italy. *Cancer Causes Control* 1991;**2**:239–46.

Sonderskov J, Olsen J, Sabroe S, Meillier L, Overvad K. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. *Am J Epidemiol* 1997;**145**:309–18.

Sonderskov J, Olsen J, Meillier L, Overvad OK, Sabroe S. The effect of transdermal nicotine patches in smoking cessation. A randomized trial in pharmacy customers in Denmark. *Ugeskr Laeger* 1999;**161**:593–7.

Stapleton JA, Russell MA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, *et al.* Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction* 1995; **90**:31–42.

Stapleton JA, Sutherland G, Russell MAH. How much does relapse after one year erode effectiveness of smoking cessation treatments? Long term follow up of randomised trial of nicotine nasal spray. *BMJ* 1998;**316**:830–1.

Sutherland G, Stapleton JA, Russell MA, Jarvis MJ, Hajek P, Belcher M, *et al.* Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992;**340**:324–9.

Sutton S, Hallett R. Randomized trial of brief individual treatment for smoking using nicotine chewing gum in a workplace setting. *Am J Public Health* 1987;**77**:1210–1.

Sutton S, Hallett R. Smoking intervention in the workplace using videotapes and nicotine chewing gum. *Prev Med* 1988;**17**:48–59.

Tonnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. *Eur Respir J* 2000;**16**:717–22.

Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnersen AB, Forchammer H, *et al.* Two and four mg nicotine chewing gum and group counselling in smoking cessation: an open, randomized, controlled trial with a 22 month follow-up. *Addict Behav* 1988;**13**:17–27.

Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnersen AB, Forchammer H, *et al.* Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. *N Engl J Med* 1988;**318**:15–18.

Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *New Engl J Med* 1991;**325**:311–15.

Tonnesen P, Norregaard J, Sawe U. Two-year outcome in a smoking cessation trial with a nicotine patch. *J Smoking Relat Disord* 1992;**3**:241–5.

Tonnesen P, Norregaard J, Simonsen K, Sawe U. [A double-blind trial of nicotine patches in smoking cessation.] *Ugeskr-Laeger* 1992;**154**:251–4.

Tonnesen P, Norregaard J, Mikkelsen K, Jorgensen S, Nilsson F. A double-blind trial of a nicotine inhaler for smoking cessation. *JAMA* 1993;**269**:1268–71.

Tonnesen P, Paoletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, *et al.* Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. *Eur Respir J* 1999;**13**:238–46.

Transdermal Nicotine Study Group. Transdermal nicotine for smoking cessation – 6-month results from 2 multicenter controlled clinical trials. *JAMA* 1991;**266**:3133–8.

Villa RS, Alvarez ABD, Hermida JRF. Eficacia de un programa multicomponente para dejar de fumar con y sin chicle de nicotina. [Effectiveness of a multi-component program to quit smoking with and without nicotine chewing gum.] *Psicol Conduct* 1999;**7**:107–18.

Wallstrom M, Nilsson F, Hirsch JM. A double-blind placebo controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. European Respiratory Society Meeting; 1997 Sep 20–24; Berlin, Germany. Abstract 2822.

Wallstrom M, Nilsson F, Hirsch JM. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. *Addiction* 2000;**95**:1161–71.

Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation: a randomized trial with telephone counseling. *Arch Intern Med* 1993;**153**:1917–23.

Wong GY, Wolter TD, Croghan GA, Croghan IT, Offord KP, Hurt RD. A randomized trial of naltrexone for smoking cessation. *Addiction* 1999;**94**:1227–37.

Zelman DC, Brandon TH, Jorenby DE, Baker TB. Measures of affect and nicotine dependence predict differential response to smoking cessation treatments. *J Consult Clin Psychol* 1992;**60**:943–52.

Studies included in the review 'A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch'[54]

Abelin T, Buehler A, Muller P, Vesanen K, Imhof PR. Controlled trial of transdermal nicotine patch in tobacco withdrawal. *Lancet* 1989;**1**:7–10.

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.

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. Lewiston, NY: Hogrefe & Huber; 1991. p. 35–46.

Allen SS, Matsukami D, Gorsline J. Cholesterol changes in smoking cessation using the transdermal nicotine system. *Prev Med* 1994;**23**:190–6.

Bertocchi F, Francucci BM. Randomized, placebo-controlled, within-patient study to evaluate the effect of repeated administration of nicotine TTS 30 cm^2, placebo and cigarette smoking on cardio-vascular sympathetic control, both in normotensive and hypertensive smokers. Basle: Ciba-Geigy Ltd; 1995. TNSI01.

Buchkremer G, Bents H, Minneker E, Opitz K. [Long-term effects of smoking cessation therapy combining behavior therapy and transdermal nicotine substitution.] *Nervenarzt* 1988;**59**:488–90.

Buchkremer G, Bents H, Horstmann M, Opitz K, Tolle R. Combination of behavioral smoking cessation with transdermal nicotine substitution. *Addict Behav* 1989;**14**:229–38.

Campbell I. Double-blind study of the efficacy of transdermal administration of nicotine (TTS) versus placebo in tobacco withdrawal in patients with chronic chest disease or cardiovascular risk. Basle: Ciba-Geigy Ltd; 1994. NI/ET2.

Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, *et al.* Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1991;**151**:749–52.

Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, *et al.* Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Monaldi Mal Torace* 1992;**47**:17–29.

Ehrsam RE, Buhler A, Muller P, Mauli D, Schumacher PM, Howald H, *et al.* Transdermal nicotine as an aid towards abstinence in young smokers. *Schweiz Rundsch Med Prax* 1991;**80**:145–50.

Fagerstrom KO, Schneider NG, Lunell E. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology* 1993;**111**:271–7.

Fiore MC, Kenford SL, Jorenby DE, Wetter DW, Smith SS, Baker TB. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest* 1994;**105**:524–33.

Foulds J, Stapleton J, Feyerabend C, Vesey C, Jarvis M, Russell MAH. Effect of transdermal nicotine patches on cigarette smoking: a double blind crossover study. *Psychopharmacology* 1992;**106**:421–7.

Foulds J, Stapleton J, Hayward M, Russell MA, Feyerabend C, Fleming T, *et al.* Transdermal nicotine patches with low-intensity support to aid smoking cessation in outpatients in a general hospital. A placebo-controlled trial. *Arch Family Med* 1993;**2**:417–23.

Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ* 1995;**311**:363–6.

Hilleman DE, Mohiuddin SM, Delcore MG. Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. *J Clin Pharmacol* 1994;**34**:222–4.

Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine-replacement therapy with use of a transdermal nicotine patch – a randomized double-blind placebo-controlled trial. *Mayo Clin Proc* 1990;**65**:1529–37.

Hurt RD, Dale LC, Fredrickson PA, Caldwell CC, Lee GA, Offord KP, *et al.* Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: one-year outcome and percentage of nicotine replacement. *JAMA* 1994;**271**:595–600.

Imperial Cancer Research Fund General Practice Research Group. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomized trial in general practice. *BMJ* 1993;**306**:1304–8.

Jorenby DE, Smith SS, Fiore MC, Hurt RD, Offord KP, Croghan IT, *et al.* Varying nicotine patch dose and type of smoking cessation counseling. *JAMA* 1995;**274**:1347–52.

Kornitzer M, Boutsen M, Thijs J, *et al.* Efficiency and safety of combined use of nicotine patches and nicotine gum in smoking cessation: a placebo controlled double-blind trial [abstract]. *Eur Respir J* 1993;**6**:630S.

Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med* 1995;**24**:41–7.

Krumpe P, Malani N, Adler J, *et al.* Efficacy of transdermal nicotine administration as an adjunct for smoking cessation in heavily nicotine addicted smokers [abstract]. *Am Rev Respir Dis* 1989;**139**:A337.

Levin ED, Westman EC, Stein RM, Carnahan E, Sanchez M, Herman S, *et al.* Nicotine skin patch treatment increases abstinence, decreases withdrawal symptoms, and attenuates rewarding effects of smoking. *J Clin Psychopharmacol* 1994;**14**:41–9.

Menard P, La Grue D. Double-blind trial versus placebo on the tolerability of transdermal nicotine application (TTS) in the cessation of smoking in patients at risk. Basle: Ciba-Geigy Ltd; 1994. NI/ET1.

Merz PG, Keller-Stanislawski B, Huber T, Woodcock BG, Rietbrock N. Transdermal nicotine in smoking cessation and involvement of non-specific influences. *Int J Clin Pharmacol Ther Toxicol* 1993;**31**:476–82.

Muller P, Abelin T, Ehrsam R, Imhof P, Howland H, Mauli D. The use of transdermal nicotine in smoking cessation. *Lung* 1990;**168**:445–53.

Mulligan SC, Masterson JG, Devane JG, Kelly JG. Clinical and pharmacokinetic properties of a transdermal nicotine patch. *Clin Pharmacol Ther* 1990;**47**:331–7.

Pullan RD, Ganesh S, Mani V, *et al.* Transdermal nicotine treatment for ulcerative colitis: a controlled trial [abstract]. *Gut* 1993;**34**:S48.

Pullan RD, Rhodes J, Ganesh S, Mani V, Morris JS, Williams GT, *et al.* Transdermal nicotine for active ulcerative colitis. *N Engl J Med* 1994;**330**:811–15.

Rennard SI, Daughton DM, Fortmann S, *et al.* Transdermal nicotine enhances smoking cessation in coronary artery disease patient [abstract]. *Chest* 1991;**100**:5S.

Rennard S, Daughton D, Cheney R, Thompson A, Miles R, Windle J, *et al.* Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 1994;**154**:989–95.

Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. *Med J Aust* 1994;**161**:130–5.

Rose JE, Levin ED, Behm FM, Adivi C, Schur C. Transdermal nicotine facilitates smoking cessation. *Clin Pharmacol Ther* 1990;**47**:323–30.

Russell MAH, Stapleton JA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, *et al.* Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ* 1993;**306**:1308–12.

Sachs DPL, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med* 1993;**153**:1881–90.

Stapleton JA, Russell MA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, *et al.* Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction* 1995;**90**:31–42.

Thomas GAO, Rhodes J, Mani V, Williams GT, Newcombe RG, Russell MAH, *et al.* Transdermal nicotine as maintenance therapy for ulcerative colitis. *New Engl J Med* 1995;**332**:988–92.

Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *New Engl J Med* 1991;**325**:311–15.

Tonnesen P, Norregaard J, Simonsen K, *et al.* The effects of a 16-hour nicotine patch in smoking cessation with a 2-year follow-up [abstract]. *Eur Respir J* 1991;**4**:504S.

Tonnesen P, Norregaard J, Simonsen K, Sawe U. [A double-blind trial of nicotine patches in smoking cessation.] *Ugeskr-Laeger* 1992;**154**:251–4.

Transdermal Nicotine Study Group. Transdermal nicotine for smoking cessation – 6-month results from 2 multicenter controlled clinical trials. *JAMA* 1991;**266**:3133–8.

Tzivoni D, Kelen A. Nicotinell TTS in patients with coronary artery disease: double-blind, between patient randomized trial of the tolerability of transdermal nicotine (Nicotinell TTS) in comparison with placebo administered for 2 weeks during a smoking cessation program: using ambulatory ECG (Holder) monitoring in patients with coronary artery disease. Basle: Ciba-Geigy Ltd; 1995. IL/T 02.

Westman EC, Rose JE. Effectiveness of a transdermal nicotine patch in smoking cessation: a double-blind, randomized, placebo-controlled trial [abstract]. *Clin Res* 1991;**39**:887A.

Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation: a randomized trial with telephone counseling. *Arch Intern Med* 1993;**153**:1917–23.

Studies included in the Cochrane Review, 'Antidepressants for smoking cessation',[42] and the review by Holm and Spencer, 'Bupropion – a review of its use in the management of smoking cessation'[13]

Ferry LH, *et al.* Enhancement of smoking cessation using the antidepressant bupropion hydrochloride [abstract]. *Circulation* 1992;**86**(4 Suppl 1):671.

Ferry LH, Burchette RJ. Efficacy of bupropion for smoking cessation in non depressed smokers [abstract]. *J Addict Dis* 1994;**13**(4):249.

Hurt RD, Sachs DPL, Glover ED, Offord KP, Johnston JA, Dale LC, *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *New Engl J Med* 1997;**337**(17):1195–202.

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New Engl J Med* 1999;**340**(9):685–91.

Hays JT, *et al.* Bupropion SR for relapse prevention (Study 406). Sixth Annual Conference of the Society for Research on Nicotine and Tobacco; 2000; Arlington, Virginia, USA. Poster presentation.

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We look forward to hearing from you.

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