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Pharmacologic-based Strategies for Smoking  
Cessation: Clinical and Cost-Effectiveness  
Analyses

*Supporting Informed Decisions*

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**Canadian Agency for Drugs and Technologies in Health**

**Pharmacologic-based Strategies for Smoking Cessation:  
Clinical and Cost-Effectiveness Analyses**

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## Conflicts of Interest

Dr. Pipe has received speaking and consulting fees from Pfizer. He has also received consulting fees from Glaxo Smith Kline and Johnson & Johnson. Dr. Pipe was involved in the following: A 12-week, double blind, placebo controlled, multicentre study with a 40 week follow-up evaluating the safety and efficacy of Varenicline Tartrate 1 mg bid for smoking cessation in subjects with cardiovascular disease. \$158,400 Pfizer Inc. (USA) 2005-08 (Principal Investigator)

STOP (Smoking Therapy for Ontario Patients) Study: The effectiveness of nicotine replacement therapy in Ontario smokers. \$3,000,000 Ministry of Health Promotion, Ontario Ministry of Health and Long-term Care, Pfizer Inc. 2005-06 (Co-investigator)

A 52-week multicentre study evaluating the safety and efficacy of Varenicline (CP-526,555) for the maintenance of smoking cessation. \$777,169 Pfizer Inc. (USA) 2003-05 (Principal Investigator)

Pilot Study of Telephone Counselling for Smokers Attempting to Quit with Nicotrol: Impact on Abstinence at Six-month Follow-up. \$36,000 McNeil Consumer Products Company. 1995

A Study to Compare the Effects of Pravastatin, Lovastatin, Simvastatin, and Placebo on Eccentric Exercise-Induced Changes in Muscle. \$199,962 Bristol-Myers Squibb. 1992-93

A Study to Compare the Effects of Simvastatin and Placebo on Eccentric Exercise-Induced Changes in Muscle. \$63,608 Bristol-Myers Squibb. 1991-92

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## ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
CAR	continuous abstinence rate
CBA	cost-benefit analysis
CCHS	Canadian Community Health Survey
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curves
CEAF	cost-effectiveness acceptability frontier
CHD	coronary heart disease
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMA	cost-minimization analysis
COPD	chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CT	controlled trial
CUA	cost-utility analysis
EVPI	expected value of perfect information
EVPII	expected value of perfect partial information
FNIHB	First Nations and Inuit Health Branch
HEED	Health Economic Evaluations Database
HUI3	Health Utilities Index Mark 3
ICER	incremental cost-effectiveness ratio
LY	life-year
MCMC	Markov Chain Monte Carlo
MCS	Monte Carlo simulation
MI	myocardial infarction
MTC	mixed treatment comparisons
NRT	nicotine replacement therapy
OCCI	Ontario Case Costing Initiative
OR	odds ratio
PPA	point prevalence abstinence
PVD-AAA	peripheral vascular disease or abdominal aortic aneurysm
PUMF	Public Use Microdata Files
QALY	quality-adjusted life-year
RCT	randomized controlled trial
TIA	transient ischemic attack
VOI	value of information

# GLOSSARY

**Continuous abstinence rate:** the proportion of people who have not smoked since the commencement of a cessation intervention.

**Cost-benefit analysis:** an economic analysis that assesses incremental costs and outcomes of alternative interventions, where cost and outcomes are measured as monetary units.

**Cost-effectiveness acceptability curves:** a set of curves representing the probability of each alternative intervention being cost-effective across a range of cost-effectiveness threshold values.

**Cost-effectiveness acceptability frontier:** a continuous or discontinuous curve representing the optimal choice of intervention (i.e., an intervention providing the highest net benefit) at each level of a range of cost-effectiveness thresholds.

**Cost-effectiveness analysis:** an economic analysis that compares incremental cost and outcomes of alternative interventions, where outcomes are measured as natural units (e.g., life-years gained, deaths avoided).

**Cost-minimization analysis:** an economic analysis that compares costs among interventions of interest.

**Cost-utility analysis:** an economic analysis that assesses incremental costs and outcomes, where outcomes incorporate health state preferences (e.g., quality-adjusted life-years).

**Deterministic sensitivity analysis:** an analysis that assesses the degree of impact of changes in one or a set of fixed input parameters on overall cost-effectiveness results.

**Dominated therapies:** interventions that are more expensive and generate less benefit compared with at least one of the other interventions being considered. Two types of dominance are strict dominance and extended dominance. A strictly dominated therapy indicates that the therapy is more expensive and generates less benefit compared with at least one of other therapies. When a therapy is dominated by extended dominance, it indicates that the therapy is more expensive and generates less benefit compared with a combination of other therapies being considered.

**EQ-5D:** a generic, multi-attribute, preference-based measure of health-related quality of life. EQ-5D consists of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, with three levels in each dimension, describing 243 unique health states. A score of one represents perfect health as defined in the EQ-5D instrument, and a score of zero represents death.<sup>1</sup>

**Expected value of partial perfect information:** an uncertainty analysis in economic modelling that quantifies the level of decision uncertainty attributable to one or a set of stochastic input parameters in economic models over total decision uncertainty.

**Expected value of perfect information:** an uncertainty analysis in economic modelling that quantifies the level of decision uncertainty by estimating opportunity cost of making an uncertain decision, given currently available information.

**Health-related quality of life:** “value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy.”<sup>2</sup> (p.22)

**Health Utilities Index Mark 3 (HUI3):** a generic, multi-attribute and preference-based measure of health-related quality of life. HUI3 consists of eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain, with five to six levels in each dimension, describing 973,000 unique health states. A score of one represents perfect health as defined in the HUI3 instrument, and a score of zero represents death.<sup>3</sup>

***Incremental cost-effectiveness ratio (ICER):*** the ratio of difference in costs (i.e., incremental costs) to difference in effectiveness (i.e., incremental effectiveness). A sequential ICER represents the ratio of incremental costs to incremental effectiveness between one intervention and the next, more expensive intervention.

***Point prevalence abstinence rate:*** the proportion of people not smoking at a particular point in time, usually expressed as “seven-day point prevalence” (have not smoked at any time in the seven days prior to the point of evaluation).

***Probabilistic analysis:*** an uncertainty analysis in economic modelling that assumes a distributional assumption to each stochastic parameter and assesses their parameter uncertainties simultaneously.

***Prolonged (sustained) abstinence rate:*** the proportion of people who have been continuously abstinent from smoking for a prolonged period preceding follow-up assessment; usually four to eight months after the end of treatment, but not necessarily since the beginning of the intervention (it includes delayed abstinence or repeated attempts to quit after the intervention).

***Quality-adjusted life-years (QALYs):*** life-years weighted by the degrees of decrement in quality of life that is associated with morbidity. QALY incorporates morbidity and mortality effects of interventions.<sup>4</sup>

# 1 INTRODUCTION

## 1.1 Background and Setting in Canada

Tobacco smoking is a risk factor for cancer, respiratory disease, and cardiovascular disease. The prevalence of smoking continues to decline. It is estimated that 19% of Canadians (approximately 5.2 million) aged 15 years and older were smokers in 2007.<sup>5</sup> Each year, approximately 45,000 Canadians die from smoking.<sup>6</sup> Significantly, one-third of Canadian smokers aged 15 years or older express an intention to quit in the next 30 days.<sup>7</sup>

Nicotine, which is the addictive chemical component of tobacco products that attracts smokers, has consequences for personal and community health. Smoking is an addiction. Although many smokers report that they quit unaided, most smokers who try to quit without smoking cessation aids are unsuccessful in the long term. In the US and UK, 70% of smokers intend to quit every year, 45% try to quit, and less than 5% are successful.<sup>8,9</sup> The rate of relapse is high among smokers who quit without treatment. The proportion who can achieve abstinence for at least one week is 25% to 51%, for at least three months is 10% to 20%, and for six months is only 3% to 5%.<sup>10</sup> There are many prescribed pharmacotherapies for smoking cessation, including nicotine replacement products, bupropion, and varenicline.

Most nicotine-dependent smokers try to ensure a “comfort level” — a sense of equilibrium that reflects ongoing stimulation or desensitization of nicotine receptors in the brain. This causes the release of dopamine in the forebrain.<sup>11</sup> A minimal exposure to nicotine changes the number and sensitivity of receptors, so that a smoker’s brain is then organized to need regular exposure to nicotine. Smokers experience discomfort (craving and withdrawal symptoms) when the levels of nicotine start to fall. The urge to smoke is also reinforced by exposure to the stimuli, settings, or situations that become associated with smoking. A cigarette is a drug-delivery device that is designed to provide a bolus of nicotine in a rapid and pleasurable fashion. Various techniques of cigarette design facilitate the rapid uptake of nicotine into the circulation. An effective and rapid method of delivering a drug is administration by inhalation. When nicotine is inhaled, it crosses the alveolar membranes of the lungs, enters the pulmonary circulation, and is rapidly delivered to the arterial system. It crosses the blood brain barrier and stimulates specific nicotine receptors in the brain stem.

In nicotine replacement therapy (NRT), non-toxic forms of nicotine delivery systems are used to provide nicotine to maintain stimulation of nicotine receptors, thereby eliminating withdrawal symptoms and the sensations of craving for nicotine during a smoking cessation attempt. It may be necessary to increase the standard doses of NRT to meet the nicotine “requirements” of a would-be non-smoker. NRT products include the nicotine patch, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine spray (unavailable in Canada), and nicotine sublingual tablets (unavailable in Canada). NRT is delivered through the skin or mucous membranes into the venous system. As a result, the levels of arterial nicotine that are produced by smoking are not equalled, while nicotine receptors can be appropriately stimulated by the steady increase in nicotine levels that occurs over a 30- to 45-minute period when NRT is delivered; for example, by the use of a patch. NRT products contain only nicotine and none of the thousands of other compounds that are present in tobacco smoke. As a result, smokers are “safer” receiving NRT

than they would be were they to continue to smoke. In 2005, the Committee on Safety of Medicines recommended that NRT be given to pregnant smokers and to adolescent smokers to help with cessation. The 2008 Cochrane review by Stead *et al.*<sup>12</sup> showed that smokers using NRT were one-and-one-half to two times more likely to be abstinent from smoking at follow-up than those receiving placebo or control treatment.

Bupropion is an atypical prescription antidepressant that inhibits the reuptake of norepinephrine and dopamine. It was found to be effective as a smoking cessation aid. The efficacy of bupropion is comparable to that of NRT. There is a small risk of seizure associated with the use of bupropion. As a result, there are contraindications to its use among those with a history of seizures or a higher likelihood of seizures (recent head injury, withdrawal from other drugs of abuse, history of bulimia).<sup>13</sup>

Varenicline is a nicotinic-receptor, partial agonist, with partial-antagonist properties. It both reduces cravings for, and decreases the pleasurable effects of, cigarettes and other tobacco products. It interacts with the alpha 4 beta 2 nicotinic acetylcholine receptor — a nicotinic receptor subtype that is thought to be responsible for the initiation and perpetuation of nicotine dependence. While occupying the receptor, varenicline's effect on it is not as pronounced as that of nicotine, and it causes an attenuated release of dopamine in the forebrain. This typically prevents the emergence of withdrawal symptoms, and thus no urge to smoke is felt. Because of its position on the receptor, varenicline prevents nicotine from occupying the site if smoking occurs. By blocking the reinforcing effects of nicotine, varenicline can produce a partial-agonist and a partial-antagonist effect. It is a prescribed medication that is used as an aid to smoking cessation. It is absorbed almost completely from the gastrointestinal tract and excreted unchanged by the kidney. It does not interact with other medications or metabolic processes. Varenicline has not been evaluated in those less than 18 years of age, pregnant women, or breastfeeding women. The Canadian Expert Drug Advisory Committee recommended that varenicline be listed as a benefit on drug formularies.<sup>14</sup> Reports suggest that there may be an increase in mood changes among those who have used varenicline, so prescribers are encouraged to monitor their patients. Those with depression or a history of depression have a higher rate of smoking. Tobacco smoke contains antidepressant substances, so smokers are continually self-administering small doses of antidepressant substances. Depression occurs with smoking cessation, irrespective of the use of cessation aids.

Behavioural support programs can play a role in the success of smoking cessation attempts. Different forms of counselling or behavioural support might increase the success rates of cessation pharmacotherapies. These programs typically involve the motivation and education of tobacco users to quit smoking by examining the results of smoking and the beneficial health effects of smoking cessation. Most smokers wish to quit and know the reasons why cessation makes sense. Assistance with quitting techniques, preparation for cessation, approaches to avoiding settings where smoking has been conditioned, and relapse management can be very helpful. Behavioural support programs include psychological interventions, telephone support, and self-help. Smoking cessation programs often combine drug treatment and behavioural support. Many clinicians recognize that the use of systematic and strategic approaches to smoking cessation help the would-be non-smoker and permit an increased likelihood of success.

## 1.2 Overview of Technology

### 1.2.1 Nicotine replacement therapy

**Nicotine transdermal patch<sup>15</sup>:** The common brand names are Habitrol, Nicoderm, Nicotrol (not in Canada), and Nicorette. The patch is supplied in different dosages ranging from 5 mg to 15 mg over 16 hours. The dosage can be adjusted to meet a smoker's nicotine requirements. The dose and duration of therapy may need to be titrated to reflect the nicotine needs and clinical circumstances of smoking patients. The product monograph treatment protocols describe a step-down (declining doses over time) approach when using NRT products. The side effects may include skin irritation (itching, redness, and stinging) at the application site, nausea, dizziness, flushing, and headache. Many of the reported side effects are often the symptoms of nicotine withdrawal.

**Nicotine gum<sup>16</sup>:** The common brand names are Nicorette and Thrive. It is available in low strength (2 mg) or full strength (4 mg). It is recommended that the gum be chewed slowly for 30 minutes. Most people typically use nine to 12 pieces of gum per day during the first month of treatment. It is recommended that daily use not exceed 24 pieces per day. The dose and duration of therapy may need to be titrated to reflect the nicotine needs and other clinical circumstances of smoking patients. According to the product monograph, the use of this product typically lasts 12 weeks. The reported side effects include mouth, teeth, or jaw problems; headache; heartburn; sweating; diarrhea; dizziness; hiccups; nausea; vomiting; and trouble sleeping.

**Nicotine lozenge<sup>17</sup>:** The common brand names are the Nicorette and Thrive lozenges. The lozenge is supplied in low strength (2 mg) or full strength (4 mg). The use of one piece every one to two hours (minimum of eight lozenges per day) in weeks one to six, one piece every two to four hours in weeks seven to nine, and one piece every four to eight hours in weeks 10 to 12 is currently recommended. The dose and duration of NRT therapy may need to be titrated to reflect the nicotine needs and clinical circumstances of smoking patients. The common side effects are similar to those of nicotine gum.

**Nicotine inhaler<sup>18</sup>:** The brand name is Nicorette inhaler. It consists of a mouthpiece and a cartridge that is loaded with 10 mg of nicotine. Each puff releases approximately 13 mcg of nicotine at room temperature. The nicotine is not delivered to the lungs, despite the name of the device. The nicotine is mainly absorbed through the oral and pharyngeal mucosa. It is recommended that six to 12 cartridges be used per day for at least three months. The dose and duration of therapy may need to be titrated to reflect the nicotine needs and clinical circumstances of smoking patients. The reported side effects include headache; nausea; mouth, tooth, or throat pain; cough; runny or stuffy nose; changes in taste; heartburn; hiccups; sweating; diarrhea; and trouble sleeping.

**Nicotine sublingual tablet<sup>19</sup>:** The common brand name is Nicorette Microtab (not in Canada), which contains 2 mg of nicotine per piece. The tablet is placed under the tongue. It is recommended that eight to 12 tablets be used per day, and that use not exceed 40 tablets per day. The reported common side effects include sore mouth or throat, dry or burning sensation of mouth, hiccups, headache, coughing, mild indigestion, and nausea.

*Nicotine nasal spray*<sup>20</sup>: The common brand name is Nicotrol NS (not in Canada). It is recommended that two to four sprays per hour be used for a usual total of eight doses (16 sprays), and that use not exceed 40 doses (80 sprays) daily. The reported side effects include nasal irritation, runny nose, sneezing, throat irritation, watering eyes, abdominal pain, acne, back pain, confusion, cough, dental problems, difficulty breathing, gas, gum problems, headache, itching, joint pain, menstrual pain or disorders, muscle aches, nausea, and palpitations.

Caution should be exercised in prescribing these nicotine replacement products to pregnant women or patients with certain medical conditions.

### **1.2.2 Bupropion**

Bupropion (amfebutamone), which has been available as an antidepressant (Wellbutrin), is also prescribed as a smoking cessation adjunct (Zyban).<sup>21</sup> The mechanism by which bupropion helps patients stop smoking is unknown. There is evidence that it may block dopamine reuptake and block serotonin and noradrenalin uptake.<sup>22</sup> Bupropion and its main metabolite also block nicotinic receptors.<sup>23,24</sup>

Bupropion is administered orally. It is available as 150 mg, film-coated, sustained-release tablets. The recommended and maximum adult dosage is 300 mg per day (150 mg twice daily). For smoking cessation therapy, dosing starts at 150 mg per day during the first three days, followed by a dose increase to 150 mg twice daily if needed. It is not indicated for use by children less than 18 years of age. Caution should be exercised when using bupropion as cessation treatment in pregnant women, elderly patients, patients with a history of seizures, patients with hepatic and renal impairment, and those with eating disorders.

The use of sustained-released bupropion is associated with a risk of seizures (approximately one in 1,000). This risk of seizures is related to dose, predisposing patient risk factors, the clinical situation, and concurrent medication use. It may be associated with the occurrence of behavioural and emotional changes, including depression and suicidal ideation. Such findings are noted when this medication is used to treat depression. The risk of suicide is higher in smokers than in non-smokers, and smoking cessation has been associated with the appearance of symptoms of depression. The US Food and Drug Administration warns that a risk of suicidality is associated with the use of bupropion, but no causal relationship has been established.<sup>25,26</sup> The most commonly observed adverse events with the use of bupropion for smoking cessation are dry mouth and insomnia.

### **1.2.3 Varenicline**

Varenicline tartrate (Champix, Chantix) is a prescription drug that is used to help adults stop smoking.<sup>27</sup> Varenicline helps to relieve the craving and withdrawal symptoms that are associated with smoking cessation. Smokers receiving varenicline feel no need to smoke, and if they do, they feel less of the sensations they ordinarily experience while smoking because nicotine is denied access to the now varenicline-occupied receptor.

Varenicline, which is administered orally, is available as film-coated tablets. The 0.5 mg tablets are white, and the 1 mg tablets are light blue. The recommended adult dosage of varenicline is

0.5 mg once daily on days one to three, 0.5 mg twice daily on days four to seven, and 1 mg twice daily from day eight through the end of a 12-week course of treatment. Its safety and efficacy has not been established in pregnancy or lactation, or for pediatric use. It should be used cautiously in geriatric patients and in patients with significant renal impairment.

The common adverse effects associated with the use of varenicline are nausea; abdominal pain; flatulence; dyspepsia; vomiting; constipation; dry mouth; insomnia; abnormal dreams; sleep disorders; headache; dysgeusia; fatigue, malaise, or asthenia; and upper respiratory tract disorders. The US Food and Drug Administration requires manufacturers to put a warning on the label of varenicline about the risk of mental health events such as changes in behaviour, hostility, agitation, depressed mood, suicidal thoughts, and attempted suicide.<sup>25,26</sup> No causal relationship has been established. The risk of suicide is higher in smokers than in non-smokers, and unaided smoking cessation has been associated with the appearance of symptoms of depression.

## 2 THE ISSUE

Most Canadian drug plans do not reimburse the cost of smoking cessation medications, although most smokers report a desire to quit. In the US, the percentage of health care plans offering full coverage for smoking cessation pharmacotherapy more than tripled from 1997 to 2002, and Medicaid programs cover smoking cessation medications in 38 states. In the UK, smoking cessation drugs are covered by the National Health Service. This raises the question of whether or not publicly funded health programs in Canada should reimburse for smoking cessation medications.

## 3 OBJECTIVES

This review compared the clinical effectiveness and cost-effectiveness of pharmacologic agents with or without behavioural support programs for smoking cessation. This included the identification of planning and equity issues as part of optimal treatment strategies. The objective was accomplished by addressing the following questions:

1. Among the general population<sup>\*</sup> of smokers, what is the comparative clinical effectiveness of varenicline, bupropion, and NRT?
2. Among the general population<sup>\*</sup> of smokers using varenicline or bupropion or NRT, what is the clinical effectiveness of adding a behavioural support program<sup>‡</sup> to drug therapy?
3. What is the impact of “free” or “paid for” pharmacotherapy on the clinical effectiveness of drugs used for smoking cessation therapy?
4. Among the general population of smokers, what is the clinical effectiveness of treating specific patient populations<sup>†</sup> with varenicline or bupropion or NRT, including a combination of these agents with behavioural support programs<sup>‡</sup>?
5. Among the general population<sup>\*</sup> of smokers, what is the cost-effectiveness of varenicline compared with that of bupropion and that of NRT?
6. Among the general population<sup>\*</sup> of smokers using varenicline or bupropion or NRT, what is the cost-effectiveness of adding a behavioural support program<sup>†</sup> to drug therapy?

7. What is the impact of copayment (of insurance claim) or payment (i.e., purchase drug as over-the-counter product) on the cost-effectiveness of drugs used for smoking cessation therapy?
8. Among smokers, what is the cost-effectiveness of treating specific patient populations<sup>‡</sup> with varenicline or bupropion or NRT, including a combination of these agents with behavioural support programs<sup>†</sup>?
9. What is the budget impact to the publicly funded drug programs of adopting the strategies that were identified as having optimal cost-effectiveness in the responses to questions 5, 6, 7, and 8?
10. What is the budget impact to the publicly funded drug programs of implementing a payment or copayment program for the strategies that were identified as having optimal cost-effectiveness in the responses to questions 5, 6, 7, and 8?
11. What is the willingness of smokers to pay for having access to strategies identified as having optimal cost-effectiveness in the responses to questions 5, 6, 7, and 8?
12. What are the general relevant planning issues related to equitable access and accountability surrounding the implementation of the treatment strategies that were identified as having, but not limited to, optimal cost-effectiveness?
13. What is the current public reimbursement status of pharmacologic agents for smoking cessation?

\*General population includes those in different age groups; groups of males, females, or both; groups of different ethnicities (i.e., First Nations and Inuit or not); as well as those undergoing initial treatment (naive) or those undergoing re-treatment (treatment-failure). The smokers in this population are relatively “healthy” — notwithstanding that smoking can be described as a chronic, relapsing addictive disorder.

<sup>†</sup>Behavioural support programs should be classified according to an Agency for Healthcare Research and Quality (AHRQ) Evidence Report<sup>28</sup> and include individual or group counselling, brief or intensive therapy (the definition of “intensive” may vary), cognitive behavioural therapy or problem-solving therapy or “12-step,” and face-to-face or telephone or internet counselling. Face-to-face counselling can occur in a pharmacy or physician’s office or involve other counsellors (e.g., face-to-face counselling based on addictions or mental health, or through social workers, or with those from faith communities).

<sup>‡</sup>Specific patient populations include those with mental illness (including opioid addiction or methadone recipients, alcohol addiction, depression, schizophrenia, and bipolar disorder), those with cardiovascular disease (including peripheral vascular disease, acute coronary syndromes, and post-myocardial infarction), those with chronic obstructive pulmonary disease (COPD), those with diabetes, those who are pregnant, as well as those who are heavy smokers (e.g., those who smoke more than 15 cigarettes a day and start smoking within 30 minutes of waking) compared with others.

## 4 CLINICAL REVIEW

### 4.1 Methods

A protocol was written before the start of the study and followed throughout the review process.

#### 4.1.1 Literature searches

Peer-reviewed literature searches were conducted for the clinical review and economic evaluation. All search strategies were developed by the information specialist with input from the project team.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, Medline In-Process & Other Non-Indexed Citations, Embase, BIOSIS Previews, and PsycINFO. The Cochrane Library was searched through the Wiley interface. The Centre for Reviews and Dissemination (CRD) databases were searched through the CRD interface. The CINAHL database was searched through the EBSCOhost interface. A parallel search was run in the Health Economic Evaluations Database (HEED). The PubMed database was also searched. CINAHL was used for clinical searches only. HEED was used only for economic searches. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search terms were varenicline, bupropion, the various forms of NRT, and smoking cessation. Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs) and systematic reviews or to economic studies. Appendix 1 shows the detailed search strategies.

The clinical and economic searches were not restricted by language or publication date. OVID AutoAlerts were set up to send monthly updates with new literature. Regular updates were performed on HEED, CINAHL, CRD databases, and The Cochrane Library databases.

The grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by handsearching the bibliographies of key papers and abstracts of conference proceedings, and through contacts with appropriate experts and agencies.

#### 4.1.2 Selection criteria

For questions 1, 2, 3, and 4, a study was eligible for inclusion only if it satisfied the following criteria:

**Study design:** An RCT with follow-up of at least six months from initiation of the treatment.

**Population:** Smokers of either general populations or specific populations:

- General population (for questions 1, 2, 3, 5, 6, and 7): those in different age groups, groups of males or females, groups with different ethnicities (e.g., First Nations and Inuit), and those undergoing initial treatment (naive) or those undergoing re-treatment (treatment-failure).

- Specific populations (for questions 3, 4, 7, and 8): those with comorbidities, mental illness (including those with an opioid dependence with or without methadone treatment, alcohol problems, depression, schizophrenia, and bipolar disorder), cardiovascular disease (including peripheral vascular disease, acute coronary syndromes, and post-myocardial infarction), COPD, diabetes, pregnant women, and heavy smokers (e.g., those who smoke more than 20 cigarettes a day).<sup>29</sup>

**Intervention:** Pharmacologic agents (NRT, bupropion, and varenicline) with or without behavioural support programs. NRT includes nicotine transdermal patches, nicotine gum, nicotine inhaler, nicotine lozenge, and nicotine sublingual tablets.

**Comparators:** Between drug class and placebo.

**Outcomes:** Biochemically verified smoking abstinence, and any treatment-related comorbidity.

**Adverse events:** All serious adverse events reported in RCTs.

#### 4.1.3 Selection method

Two reviewers (KT, KC) independently applied the selection criteria and screened all citation titles and abstracts that were retrieved from the literature search. The full texts of all articles that appeared to meet the selection criteria were ordered. The reviewers then independently reviewed the full text and selected articles based on the selection criteria (flow diagram is shown in Appendix 2). Duplicate publications were excluded if information was redundant. The differences between reviewers were resolved by discussion and consensus.

#### 4.1.4 Data extraction strategy

Data from the selected articles were independently extracted by reviewers (KT, KC) using the predesigned data extraction form (Appendix 3). The discrepancies in data extraction between reviewers were resolved by discussion.

#### 4.1.5 Strategy for validity assessment

The quality of the included trials for questions 1 to 4 was independently evaluated by reviewers (KT, KC) using a combination of the Jadad scale<sup>30</sup> and the Hailey scale.<sup>31</sup> The differences were discussed and resolved by consensus. The quality of the study was rated on a scale ranging from A to E, where A (overall score 11.5 to 15.0) indicates high quality with a high degree of confidence in study findings, B (overall score 9.5 to 11.0) indicates good quality with some uncertainty regarding the study findings, C (overall score 7.5 to 9.0) indicates fair to good quality with some limitations that should be considered in any implementation of the study findings, D (overall score 5.5 to 7.0) indicates poor to fair quality with substantial limitations in the study findings and should be used cautiously, and E (overall score 1.0 to 5.0) indicates poor quality with unacceptable uncertainty for study findings. The ratings are based on aspects of study design and study performance, and are applicable to both randomized and non-randomized studies (Appendix 3). The results of the quality assessment were used to study the impact of the trial quality on the pooled estimates, and subgroup analysis was performed if deemed necessary.

#### 4.1.6 Data analysis methods

##### a) Overview

The studies were classified based on trial populations and relevant comparisons. Before the quantitative pooling of study-specific outcomes, a qualitative analysis was undertaken. This qualitative analysis involved an evaluation of the clinical heterogeneity of included studies based on patient baseline characteristics and study characteristics. If substantial heterogeneity existed in certain comparisons (behavioural) or in a subset of studies (unusual placebo groups), then only qualitative reviews of findings were reported.

##### b) Bayesian multiple treatment comparisons

If meta-analysis was deemed appropriate, a Bayesian random effects modelling technique referred to as mixed treatment comparisons (MTC)<sup>32</sup> meta-analysis was employed. MTC meta-analysis is a generalization of a standard meta-analysis for pairwise trials to a simultaneous analysis of multiple pairwise comparisons. Given the network of direct comparisons across the range of interventions, both direct and indirect evidence available for pairwise comparisons can be obtained from a simultaneous analysis with MTC meta-analysis. For instance, a meta-analysis of placebo-controlled drug-A trials (PA) provides a direct estimate of the true relative effect of A versus placebo ( $d_{PA}$ ). A meta-analysis of PB trials provides a direct estimate of the true relative effect  $d_{PB}$ . A meta-analysis of AB trials provides a direct estimate of the true relative effect ( $d_{AB}$ ). In addition, the intervention C is included and direct estimates from AC trials are available ( $d_{AC}$ ). However, direct estimates for  $d_{BC}$  and  $d_{PC}$  are not available. With a simultaneous analysis using MTC meta-analysis, direct and indirect estimates can be obtained for  $d_{PA}$ ,  $d_{PB}$ ,  $d_{AB}$ ,  $d_{AC}$ ,  $d_{BC}$ , and  $d_{PC}$ . Song et al.<sup>33</sup> and Vandermeer et al.<sup>34</sup> found that similar conclusions are derived from indirect comparisons compared with syntheses of direct comparisons.

Modern Bayesian approaches enable the flexible computation of MTC meta-analysis based on either all or various chosen subsets of the available studies, as well as with or without random effects and/or adjustments for potential sources of heterogeneity (meta-regression). They conveniently provide credible intervals (CrIs) for the various treatment comparisons of interest and probability-based assessments of which interventions are superior to others. In all meta-analyses that were performed, random study treatment effects were assumed, and the consistency of direct and indirect evidence for each comparison was investigated as thoroughly as possible.<sup>35</sup>

As a first step in the analysis, standard frequentist fixed or random effects modelling was used to meta-analyze derived pairwise estimates based on the included trials, providing a useful sensitivity analysis in a more familiar format. The next step was to code the design matrix in a standard logistic regression analysis to provide a classical MTC-based fixed effects pooled confidence interval (CI). These could be interpreted as Bayesian CrIs based on completely uninformative prior assumptions. Bayesian pooled CrIs for fixed effects were then calculated and compared to the classical fixed CIs. Finally, these Bayesian pooled fixed effects CIs were compared to the Bayesian pooled random effects CrIs that were used in the primary analyses. In this way, the robustness (or lack thereof) of the path from no prior information and no random effects to prior information and random effects was evaluated. Robustness would be demonstrated if the Bayesian and classical pooled fixed effects intervals were similar and the Bayesian pooled random effects were wider, but not extremely so. Unfortunately, the use of

MTC random effects intervals, both classical and Bayesian, is a current area of active research, and some uncertainty in the correctness of the intervals is unavoidable.

If sufficient data were available, subgroup analysis and/or meta-regression techniques were employed to assess the impact of potentially important sources of heterogeneity, including both study design features and aggregated patient characteristics. Additional sensitivity analyses dealing with outlying data points and study quality and other factors were also considered to establish the robustness of findings. Analyses of dichotomous outcomes were summarized using odds ratios (ORs) and 95% CrIs. To ensure the overall effects are dominated by data from the trials and not influenced by choice of initial (prior) distribution, low information (non-informative) priors were used — that is, the vague normal prior distributions centred at 0 with adequately large variances used for log OR, and uniform prior distributions were used for between-study variance parameters. For fixed effects assumptions, the authors of this report were able to rule out large influences of prior data by direct comparison with classical methods that use no prior information. The purpose of these prior distributions was not to incorporate salient “extra-data” information into the analysis, but, instead, to provide CrIs that have good repeated sampling properties often equal or superior to classical CIs.<sup>36</sup> Various sensitivity analyses might deviate from this — purposefully incorporating salient “extra-data” information and meaningfully interpreting the CrI as probability intervals.

**c) Estimation methods and software**

All evidence syntheses were performed using Gibbs sampling via Markov Chain Monte Carlo (MCMC) methods implemented using WinBUGS software. Appropriately sized burn-in periods and iteration periods were employed for all syntheses. As previously outlined, convergence and the robustness of the prior information were further assured by direct comparison to the use of classical methods with no prior information. Raw study data and model-based forest plots were presented for all evidence syntheses to supplement reported estimates.

The analysis strategy adopted here was to start with very simple basic models, and step by step, replace these with more efficient though somewhat more complex and hence less robust models. This approach allows assessment of when the assumptions that are needed for the more complex models become important for the validity of the findings. The planned primary assessment was the fully Bayesian MTC random effects model. The final assessment will focus primarily on the pooled credible intervals and what effects they include. Assessment of how the findings changed between various models was based on a visual inspection for any practical differences between the resulting CIs and CrIs. Similar to the investigation of study heterogeneity, the power of formal tests to detect this “model heterogeneity” is likely to be low, and a graphical comparison was considered to be more suitable.<sup>37</sup>

The first step in this strategy was the meta-analysis of direct (head-to-head) comparisons using what was available from the trials. It was done using statistical methods and RevMan software from The Cochrane Collaboration<sup>38</sup> that are well understood and widely documented. The second step was to include the indirect evidence — an approach called MTC. Bayesian methods are traditionally used to undertake this, but a design matrix was specially coded so that the mixed treatment comparisons could be made using standard logistic regression software. The resulting CIs are understood to have the appropriate frequency-based CI coverage. All the logistic

regressions were carried out using R software.<sup>39</sup> In addition, the direct comparisons initially performed using RevMan software were rerun using the R package “meta.”<sup>40</sup>

Next, a Bayesian analysis was undertaken using the fitted values from the logistic regression program to better ensure convergence and to show the effect of the prior information being added. To make this comparison, the Bayesian analysis was first done under the fixed effects assumption to most closely match the logistic regression model (i.e., exact same data model or likelihood with only the addition of a prior). As the final step, a fully Bayesian MTC random effects model (using the methodology and program scripts of the University of Bristol’s Community Based Medicine group [<https://www.bris.ac.uk/cobm/research/mpes/mtc.html>]) was undertaken using MCMC methods implemented in WinBugs software.<sup>41</sup> Each analysis script was run five times, using a different MCMC chain to assess convergence. All the analyses were automated using R and WinBugs software and the R2WinBUGS package<sup>42</sup> and run many times. A final run was undertaken and saved with an MCMC sample size of 100,000 for each of the five runs (a total of 500,000 draws).

Convergence is always a concern when using WinBUGS or other MCMC software. The resulting intervals were compared against the RevMan “direct evidence only” pooled CIs, then the logistic regression-based mixed treatment evidence pooled CIs, and finally, the Bayesian fixed effects pooled CIs. If all models support the same clinical conclusions, not only is MCMC convergence being checked, but a high degree of robustness to the different modelling assumptions is being demonstrated. That is, the conclusions will have followed from the simplest model, while none of the more complex models suggested anything different. This analysis strategy is sometimes called “scaffolding.” In addition, the evaluation or documentation of the CI coverage of Bayesian CrIs is being suggested more often by Bayesian statisticians<sup>43</sup> and is currently recommended by the US Food and Drug Administration or FDA.<sup>44</sup>

The output from the logistic regression MTC and Bayesian comparisons were summarized in tables that provide the log OR and standard errors from the logistic regression and the Bayesian random effects models, along with the 95% CI for the OR and the 95% CrI for the OR. The CrIs from the Bayesian fixed effects model were plotted alongside the CIs from the logistic regression mixed treatment model for manual comparison. In addition, the probability of a treatment being the best treatment (among those included in an MTC) was also estimated. This was tabulated from the number of times in the MCMC samples that a treatment was observed to be best (a more positive treatment effects parameter). Formal Bayesian hypothesis testing was thought to be unnecessary, and it was not attempted — the CrIs (and CIs) provide a sufficient assessment and summary of the available evidence.

Meta-regression was not attempted, because there was no strong prior concern about one or two particularly important covariates. More importantly, the arguments to rule out ecological bias (a confounded or even reversed appearance of an effect due to the use of study covariate summaries instead of actual covariates values<sup>45</sup>) were lacking.

#### **d) Comparison between interventions**

The effects of NRT, bupropion, and varenicline were compared with those of placebo. The nicotine replacement products (patch, gum, lozenge, spray, sublingual, or inhaler) were analyzed separately and compared with each other and with bupropion and varenicline.

Smoking abstinence rates were pooled separately based on the length of follow-up (e.g., six months or one year) and the type of abstinence reported in the trials; for example, point prevalence abstinence, continuous abstinence, and prolonged abstinence. Different patient populations were studied separately. Pooled estimates on behavioural support were obtained from trials that were judged to be related. Otherwise, the results of individual trials were reported separately using a qualitative approach.

## **4.2 Results**

### **4.2.1 Quantity of research available**

From the 3,528 citations (Appendix 2) that were identified in the original literature search, 354 potentially relevant reports were retrieved for scrutiny. Eight reports were retrieved from hand-searching and the grey literature search. A total of 155 articles describing 143 trials were selected for inclusion. During the review process, a new trial<sup>46</sup> was identified. It assessed the relative efficacies of five smoking cessation pharmacotherapy interventions using placebo-controlled, head-to-head comparisons. This trial was not included in the analysis, but its results appear in the outcomes of the combined therapy section.

Some of the included studies were presented in multiple publications that described different aspects of the trials or preliminary results. Unless otherwise indicated, the main publication, which described the most recent and comprehensive study outcomes, was selected for citation and for quality assessment. Appendix 4 lists the included studies. The network diagrams joining placebo-controlled trials and head-to-head comparison trials of different pharmacotherapies appear in Appendix 5.

### **4.2.2 Study characteristics**

The included trials for questions 1, 2, and 4 were classified into four main categories: varenicline, NRT, bupropion, and combined therapy. Three trials were included for question 3. The study and patient baseline characteristics of each study appear in Appendix 6. Most of the study populations smoked 10 or more cigarettes per day.

#### **a) Varenicline**

Among the 10 trials of varenicline, six were of varenicline versus placebo, three were of varenicline versus bupropion versus placebo, and one studied varenicline versus nicotine patch.

#### **Varenicline versus placebo**

All six trials were double-blinded, parallel, and multicentred, from Japan;<sup>47</sup> the US;<sup>48,49</sup> Korea and Taiwan;<sup>50</sup> China, Singapore, and Thailand;<sup>51</sup> and the US and Australia.<sup>52</sup> Pfizer sponsored all the trials.

Most studies had treatment duration of 12 weeks. Varenicline dosage varied from 0.25 mg to 1.0 mg twice daily. Self-help booklets and brief counselling were provided in addition to pharmacotherapy.

The study populations of all trials (N = 2,529) consisted of relatively healthy and motivated-to-quit adult smokers between 18 and 75 years of age. Smokers with serious diseases or those undergoing substance abuse were excluded.

One trial<sup>53</sup> was published in January 2010 while this report was being reviewed. This trial compared the efficacy and safety of varenicline with placebo for smoking cessation in 714 smokers with stable cardiovascular disease, along with counselling for 12 weeks and follow-up of 52 weeks.

### **Varenicline versus bupropion versus placebo**

All three trials were double-blinded, parallel, multicentred, conducted in the US, and sponsored by Pfizer.<sup>54-56</sup>

The treatment duration was 12 weeks in two trials<sup>54,55</sup> and seven weeks in one trial.<sup>56</sup> The full strengths of varenicline and bupropion were 1 mg and 150 mg twice daily, respectively. Self-help booklets and brief counselling were provided in addition to pharmacotherapy.

The participants in all three trials (N = 2,690) were motivated-to-quit, healthy adult smokers, 18 to 75 years of age. Pregnant women and smokers with serious or unstable diseases or substance abuse were excluded.

### **Varenicline versus nicotine patch**

The one trial<sup>57</sup> was open label, multicentred, multinational (US, UK, Belgium, France, and The Netherlands), and was sponsored by Pfizer.

The treatment duration was 12 weeks of varenicline and 10 weeks of nicotine patch, with tapering doses during the last four weeks of treatment when the primary end point was measured. The full strength of varenicline was 1 mg twice daily. Nicotine patch was used at 21 mg daily for six weeks, 14 mg daily for the next two weeks, and 7 mg daily for the last two weeks. The participants (N = 757) were relatively healthy adult cigarette smokers between 18 and 75 years of age. Pregnant smokers, nursing mothers, and those with serious diseases were excluded.

### **b) NRT**

Among the 59 trials of NRT versus placebo, there were 19 trials of NRT versus NRT (with or without behavioural support), 10 trials of NRT plus behavioural support versus usual care, and 14 trials of NRT plus behavioural support versus behavioural support.

### **NRT versus placebo**

Among the 59 trials of NRT versus placebo, 23 trials focussed on nicotine patch, 23 on nicotine gum, one on nicotine lozenge, three on nicotine sublingual tablets, five on oral nicotine inhaler, and four on nicotine nasal spray.

**Nicotine patch versus placebo:** Of the 23 trials, 13 were conducted in the US,<sup>58-70</sup> four in the UK,<sup>71-74</sup> one in Croatia,<sup>75</sup> one in Italy,<sup>76</sup> one in Australia,<sup>77</sup> two in Denmark,<sup>78,79</sup> and one in 17 European countries.<sup>80</sup> Sixteen trials were sponsored by pharmaceutical companies,<sup>58,59,61,62,64,66,68,69,71-74,76-78,80</sup> five trials reported that industry provided all

patches,<sup>63,65,67,75,79</sup> one trial did not report the source of funding,<sup>60</sup> and one trial received non-industry funding.<sup>70</sup>

The treatment duration ranged from three to 18 weeks. For treatments of more than three weeks, the nicotine patches were usually started at full dose for three to four weeks, followed by tapering. In addition to pharmacotherapy, four trials<sup>58,62,65,72</sup> provided a self-help booklet, six trials<sup>61,63,66,67,69,77</sup> provided a self-help booklet and group behavioural counselling, eight trials<sup>59,64,68,70,73,74,76,79</sup> provided a self-help booklet and brief counselling (individual or group), and five trials<sup>60,71,75,78,80</sup> provided no additional support.

The study populations included hospital inpatients and outpatients (N = 358) in two trials,<sup>66,71</sup> smokers with a history of alcoholism (N = 115) in one trial,<sup>63</sup> pregnant women (N = 250) in one trial,<sup>79</sup> and relatively healthy smokers (N = 11,773) in the remaining trials. Most participants were motivated-to-quit adult cigarette smokers who were 18 years of age or older.

**Nicotine gum versus placebo:** Of the 23 trials, 11 were conducted in the US,<sup>81-91</sup> three in the UK,<sup>92-94</sup> three in Sweden,<sup>95-97</sup> one in Denmark,<sup>98</sup> one in Thailand,<sup>99</sup> one in Germany and Switzerland,<sup>100</sup> one in Iceland,<sup>101</sup> one in France,<sup>102</sup> and one in Venezuela and Sweden.<sup>103</sup> The pharmaceutical companies provided funding to five trials,<sup>91,94,97,99,100</sup> and study medication to eight trials.<sup>81,87-89,92,93,98,102</sup> Three trials received public funding.<sup>85,86,101</sup> Three trials received public and pharmaceutical funding,<sup>83,84,90</sup> and four trials did not report the source of funding.<sup>82,95,96,103</sup>

The treatment duration varied from four weeks to 12 months. The gum was first used on an as-needed basis, followed by a weaning period. In addition to pharmacotherapy, participants received a self-help booklet and behavioural support (group or individual),<sup>81,82,85,86,89,95-98,101,103</sup> a self-help booklet and brief counselling,<sup>84,87,88,94</sup> a self-help booklet only,<sup>83,99</sup> or no additional support.<sup>90-93,100,102</sup>

The study populations included smokers with and without a history of major depressive disorders (N = 809) in two trials,<sup>86,88</sup> smokers with smoking-related disorders (chronic bronchitis, emphysema, asthma, and cardiovascular disease) (N = 206) in one trial,<sup>96</sup> pregnant smokers (N = 194) in one trial,<sup>89</sup> and relatively healthy smokers (N = 9,002) in the remaining trials. Most participants were motivated-to-quit adult (18 years of age or older) cigarette smokers.

**Nicotine lozenge versus placebo:** The one trial<sup>104</sup> was multicentred and conducted in the US and UK. It was funded by a pharmaceutical company. The treatment duration was up to 24 weeks. The study population (N = 1,818) consisted of adult motivated-to-quit smokers, who were stratified into low- and high-nicotine dependence based on the Fagerström Test for Nicotine Dependence scores.

**Nicotine sublingual tablet versus placebo:** The three trials came from the US,<sup>105</sup> Denmark,<sup>106</sup> and Sweden.<sup>107</sup> The US trial was funded by a pharmaceutical company, the Danish trial received both public and industry funding, and a pharmaceutical company provided all the tablets for the Swedish trial.

The treatment with full dose was set for three months, followed by a tapering period of three to six months. All participants received a self-help booklet and brief counselling in addition to medication.

In one trial,<sup>106</sup> the study population consisted of patients with COPD (N = 370). Two trials<sup>105,107</sup> included relatively healthy smokers (N = 488). Most participants were motivated-to-quit adult (18 years of age or older) cigarette smokers.

**Oral nicotine inhaler versus placebo:** Of the five included trials, one was conducted in Switzerland,<sup>108</sup> one in Sweden,<sup>109</sup> two in the US,<sup>110,111</sup> and one in Denmark.<sup>112</sup> Four trials<sup>108,109,111,112</sup> reported that funding was received from pharmaceutical companies. One trial did not report its source of funding.<sup>110</sup>

The treatment duration varied from six to 18 months. Treatment was provided on an as-needed basis, followed by a tapering period. After approximately three months of therapy and during the tapering period, participants were encouraged to reduce the dose. Participants in three trials<sup>108,109,112</sup> received counselling or behavioural support. Those in two trials<sup>110,111</sup> received no support intervention in addition to pharmacotherapy.

Most participants in all five trials (N = 1,585) were relatively healthy and motivated-to-quit adult (18 years of age or older) cigarette smokers.

**Nicotine nasal spray versus placebo:** Of the four trials, one each was conducted in Iceland,<sup>113</sup> Sweden,<sup>114</sup> the US,<sup>115</sup> and the UK.<sup>116</sup> Three trials<sup>113-115</sup> were funded by pharmaceutical companies. One trial<sup>116</sup> received public and industry funding.

Treatment was given on an as-needed basis with a maximum of five doses per hour, and not exceeding 40 doses per day. Participants received a self-help booklet and group behavioural support in three trials,<sup>113,114,116</sup> and a self-help booklet only in one trial.<sup>115</sup>

The study populations of all four trials (N = 937) consisted of relatively healthy and motivated-to-quit adult (18 years of age or older) cigarette smokers.

### **NRT versus NRT with or without behavioural support**

Among the 19 trials, there were two trials of nicotine patch versus nicotine nasal spray, one trial of nicotine patch versus nicotine gum versus placebo, one trial of nicotine lozenge versus nicotine gum, one of nicotine patch versus nicotine inhaler, one of nicotine spray versus nicotine gum versus nicotine inhaler, eight trials of nicotine patch versus nicotine patch plus behavioural support, and five trials of nicotine gum versus nicotine gum plus behavioural support.

**Nicotine patch versus nicotine nasal spray:** The two trials were conducted in the US.<sup>117,118</sup> One trial<sup>117</sup> received public funding, and the other<sup>118</sup> received funding from both public and industry sources. The treatment duration varied from six to 12 weeks. Participants in one trial<sup>118</sup> received group behavioural counselling in addition to pharmacotherapy. Most participants in the two trials (N = 1,683) were relatively healthy and motivated-to-quit adult (18 years of age or older) cigarette smokers.

***Nicotine patch versus nicotine gum versus placebo:*** The one trial<sup>119</sup> that was performed in the US received public funding. The treatment duration was 12 weeks. The study population included motivated-to-quit adolescent smokers (N = 120) between 13 and 17 years of age, with no major physical health problems. All participants received brief individual counselling and group behavioural therapy in addition to pharmacotherapy.

***Nicotine lozenge versus nicotine gum:*** The one trial<sup>120</sup> was conducted in the US and was supported by public funding. Participants were randomized to receive lozenge or gum, and to use a quit line or self-help program for eight weeks. Most participants (N = 408) were relatively healthy adults and motivated-to-quit smokers.

***Nicotine patch versus nicotine inhaler:*** The one trial<sup>121</sup> was conducted in Denmark and was supported by a pharmaceutical company. Participants were patients with lung problems, recruited from a lung clinic in a low-resource set-up. They were adult, motivated-to-quit smokers (N = 446). The NRT was recommended to be used up to three months, with a possibility of continuing use for up to nine months on an individual basis. All participants received counselling from nurses.

***Nicotine mouth spray versus nicotine gum versus oral nicotine inhaler:*** The study population of one trial<sup>122</sup> that was conducted in South Africa included 100 participants of relatively healthy adults and motivated-to-quit smokers. Pharmacotherapy occurred for three months with no additional intervention. The trial received industry funding.

***Nicotine patch versus nicotine patch plus behavioural support:*** Seven out of eight included trials were conducted in the US,<sup>123-129</sup> and one trial was in The Netherlands.<sup>130</sup> Six trials reported receiving financial support from public funding.<sup>123,124,127-130</sup>

The treatment duration was eight to 12 weeks. The behavioural support varied between trials and included a help line, brief counselling (face-to-face or telephone), or intense cognitive behavioural support.

The study populations included patients who were admitted to the observation unit with chest pain (N = 543) in one trial,<sup>124</sup> hospitalized patients (N = 223) with various comorbidities in one trial,<sup>127</sup> cardiovascular outpatients (N = 385) in one trial,<sup>130</sup> low-income women (N = 214) in one trial,<sup>128</sup> and relatively healthy subjects (N = 818) in three trials.<sup>123,125,126</sup> All participants were adult, motivated-to-quit cigarette smokers.

***Nicotine gum versus nicotine gum plus behavioural support:*** All five trials were conducted in the US.<sup>85,131-134</sup> Four were publicly funded,<sup>85,131-133</sup> and one was supported by a pharmaceutical company.<sup>134</sup> Three trials<sup>85,131,132</sup> did not report treatment duration. Participants in two trials received treatment for seven weeks<sup>134</sup> and up to six months.<sup>133</sup> The behavioural support consisted of a self-help program or behavioural treatment.

Participants in all five trials (N = 1,205) were relatively healthy and motivated-to-quit adult smokers.

### **NRT (and/or bupropion) plus behavioural support versus usual care**

Among the 10 included trials, three were conducted in Australia,<sup>135-137</sup> four in the US,<sup>66,138-140</sup> one in Canada,<sup>141</sup> one in the UK,<sup>142</sup> and one in Spain.<sup>143</sup> Five trials received financial support from public funding,<sup>135-137,139,140</sup> two trials were sponsored by pharmaceutical companies,<sup>66,144</sup> one trial received public and industry funding,<sup>143</sup> and two trials did not report their source of funding.<sup>138,141</sup>

The interventions varied from three weeks (one trial<sup>66</sup>) to six to 12 weeks (eight trials<sup>135,137-143</sup>). One trial<sup>138</sup> used NRT and/or bupropion in the active treatment arm. Behavioural support in addition to pharmacotherapy was provided by physicians or nurses to those in the active treatment arm. Participants in the usual care or control arm received neither pharmacotherapy nor formal information about smoking cessation.

The six trials<sup>66,136,138,140-142</sup> included 2,457 hospitalized patients. Other specific populations included those with a psychotic disorder<sup>135</sup> (N = 298), substance abuse<sup>139</sup> (N = 225), and cancer<sup>137</sup> (N = 137). One trial included relatively healthy participants.<sup>143</sup> All participants were motivated-to-quit adult smokers.

### **NRT plus behavioural support versus behavioural support**

Of the 14 trials that met the inclusion criteria, nine trials were conducted in the US,<sup>145-153</sup> one in Canada,<sup>154</sup> two in the UK,<sup>142,155</sup> one in Australia,<sup>156</sup> and one in Italy.<sup>157</sup> Thirteen trials received public funding, and one trial<sup>142</sup> reported receiving industry financial support.

The treatment duration of NRT and behavioural support and the type of behavioural support varied between trials.

The study populations included hospitalized patients (N = 427) in two trials,<sup>142,155</sup> recovering alcoholics (N = 205) in one trial,<sup>148</sup> low-income housing smokers (N = 173) in one trial,<sup>151</sup> pregnant smokers (N = 181) in one trial,<sup>153</sup> and relatively healthy smokers (N = 2,266) in nine trials.<sup>145-147,149,150,152,154,156,157</sup> All participants were motivated-to-quit adults.

### **c) Bupropion**

#### **Bupropion versus placebo**

Of the 23 trials that met the inclusion criteria, 15 trials were conducted in the US,<sup>158-172</sup> one in France,<sup>173</sup> one in Italy,<sup>174</sup> one in Brazil,<sup>175</sup> one in New Zealand,<sup>176</sup> one in the Netherlands,<sup>177</sup> and three in multiple countries.<sup>178-180</sup> Nine trials were financially supported by industry;<sup>163,165,167,171,173,176,178-180</sup> 11 trials received public funding, with study medication from pharmaceutical companies;<sup>158,159,161,162,164,168,169,172,174,177,181</sup> two trials received public and industry funding,<sup>166,170</sup> and one trial did not report its source of funding.<sup>175</sup>

The treatment duration of bupropion varied from six to 12 weeks. Bupropion was usually administered at 150 mg daily for the first three to six days of treatment, followed by 150 mg twice daily for the rest of the treatment course. In addition to pharmacotherapy, group behavioural therapy was given to participants in six trials,<sup>158-162,164</sup> and brief counselling (face-to-face or telephone) in 16 trials.<sup>163,165-171,173-180</sup> One trial<sup>172</sup> added cognitive behavioural intervention (individual and telephone counselling) to pharmacotherapy.

The study populations included patients with schizophrenia (N = 103) in three trials,<sup>160-162</sup> patients with chronic post-traumatic stress disorder (N = 15) in one trial,<sup>166</sup> adolescents (N = 312) in one trial,<sup>169</sup> inpatients or outpatients with comorbidities (N = 959) in three trials,<sup>170,172,179</sup> COPD patients (N = 586) in two trials,<sup>171,177</sup> and relatively healthy subjects (N = 6,101) in 13 trials.<sup>158,159,163-165,167,168,173-176,178,180</sup> All participants were motivated-to-quit smokers.

### **Bupropion versus nicotine patch**

The included trial was from Turkey.<sup>182</sup> The source of funding was not reported. The population consisted of motivated-to-quit adult cigarette smokers (N = 100) who received medication treatment for six weeks. All participants were relatively healthy.

### **Bupropion versus bupropion plus behavioural support**

The one trial was conducted in the US<sup>168</sup> and supported by public funding. The study medication was provided by industry. The treatment course of bupropion lasted nine weeks. The intervention support was brief individual counselling. The study population in the two arms (N = 229) included adult motivated-to-quit smokers with no serious diseases who were neither pregnant nor nursing mothers.

#### **d) Combined pharmacotherapy**

##### **Combined NRT**

**Nicotine patch plus nicotine spray versus nicotine patch:** The one trial conducted in Iceland<sup>183</sup> evaluated the efficacy of using a nicotine patch for five months and nicotine nasal spray for one year. The trial was funded by a pharmaceutical company. Additional intervention support was not mentioned. The participants (N = 239) were adults and motivated-to-quit cigarette smokers who had no serious medical conditions.

**Nicotine inhaler plus nicotine patch versus nicotine inhaler:** The one trial conducted in France<sup>184</sup> compared the efficacy of nicotine inhaler plus nicotine patch versus nicotine inhaler plus placebo patch for smoking cessation. The trial received financial support from a pharmaceutical company. The treatment duration was 26 weeks, with no additional intervention support. The participants (N = 400) were motivated-to-quit adult cigarette smokers with no serious medical conditions.

**Nicotine patch plus nicotine gum versus nicotine patch:** One trial<sup>185</sup> was conducted in Belgium and Sweden. It was sponsored by a pharmaceutical company. It evaluated the possible beneficial effects of adding nicotine gum to the routine of participants using nicotine patch. Medication was given for 24 weeks with no additional intervention support for smoking cessation. The participants (N = 374) were motivated-to-quit adult smokers and relatively healthy.

The other trial<sup>186</sup> that was conducted in the US was supported by public funding. It compared the efficacy of smoking cessation treatment using a combination of nicotine patch plus nicotine gum versus nicotine patch plus placebo gum in alcohol-dependent participants. The participants were relatively healthy and motivated-to-quit adult cigarette smokers being treated for alcohol dependency.

##### **Combined NRT and bupropion**

**Bupropion plus nicotine gum versus bupropion versus placebo:** The one trial conducted in the US<sup>187</sup> was supported by public funding. It determined the efficacy of bupropion and nicotine

gum in combination, bupropion, and a placebo in promoting smoking cessation. The treatment duration was nine weeks, with three sessions of brief counselling. The participants (N = 608) were motivated-to-quit cigarette smokers with no serious medical conditions.

***Bupropion plus nicotine patch versus bupropion versus nicotine patch versus placebo:*** The one trial was conducted in the US<sup>188</sup> and was sponsored by a pharmaceutical company. The treatment duration was nine weeks with brief individual counselling for smoking cessation in addition to medication. The population consisted of relatively healthy and motivated-to-quit adult cigarette smokers (N = 893).

***Bupropion plus nicotine patch plus nicotine inhaler versus nicotine patch:*** The one trial was conducted in the US<sup>189</sup> and was supported by public funding. The treatment duration was 10 weeks on nicotine patch, while nicotine oral inhaler was used on an as-needed basis and was given on an ad-libitum basis. Bupropion was discontinued in the following two weeks if participants continued to feel comfortable. No additional intervention support was provided. The study population consisted of medically ill smokers (N = 127) with various comorbidities, such as cardiovascular and vascular disease, pulmonary disease, cancer, hypertension, diabetes, hyperlipidemia, and pulmonary infections.

***NRT plus bupropion versus NRT:*** Of the four included trials, one was conducted in Canada,<sup>190</sup> and three were in the US.<sup>191-193</sup> All received public funding. The treatment duration varied from seven to 12 weeks. Behavioural support (group or individual counselling) was provided in addition to pharmacotherapy in all trials. The populations included patients with schizophrenia (N = 109) in two trials,<sup>190,191</sup> adolescents (N = 211) in one trial,<sup>192</sup> and smokers recruited from Veterans Affairs (N = 244) in one trial.<sup>193</sup>

#### **e) *No pay versus pay (or incentives)***

Of three trials that met the inclusion criteria, two were conducted in the US<sup>62,194</sup> and the other was in The Netherlands.<sup>195</sup> Two trials were funded by pharmaceutical companies<sup>62,195</sup> and one received public funding.<sup>194</sup> Hays et al. (1999)<sup>62</sup> compared the efficacy of no-pay versus pay for over-the-counter nicotine patch to be used in smoking cessation. Kaper et al. (2005)<sup>195</sup> compared the effects of financial reimbursement with those of no reimbursement for all smoking cessation treatments, including bupropion, NRT, and behavioural counselling. Volpp et al. (2009)<sup>194</sup> assessed the financial incentives for smoking cessation among employees of a multinational company that was based in the US. All participants in this trial received information about community-based smoking cessation resources and the standard health benefits provided by the firm. Participants (N = 2,841) in the three trials were motivated-to-quit adult smokers and relatively healthy.

### **4.2.3 Data analyses and synthesis**

The quality assessment scores of the included trials appear in Appendix 7. The outcomes data were grouped, analyzed, and synthesized in order to provide answers to the research questions. The details from all analyses appear in the appendices. The important differences are highlighted in the main text, and figures are provided to summarize some of the findings.

The results were consistent across all models. The available indirect evidence (that was not used in the standard Cochrane-based approach) did not have a large impact. The addition of prior information had little impact — the Bayesian fixed effects CrIs were almost identical to the logistic regression MTC CIs — except when the events were rare. This happened for some adverse events, where the Bayesian CrIs were more sensible (as expected based on literature). The Bayesian random effects CrIs were slightly wider, as would be expected from the allowance of random effects, displaying the relative homogeneity of effects estimates (allowance for heterogeneity had moderate to little impact).

**a) Among the general population of smokers, what is the comparative clinical effectiveness of varenicline, bupropion, and NRT?**

**Monotherapy**

**Quality assessment**

**Varenicline:** Six trials comparing varenicline and placebo,<sup>47-52</sup> three comparing varenicline with bupropion and with placebo,<sup>54-56</sup> and one comparing varenicline with nicotine patch<sup>57</sup> included smokers with no serious medical conditions. All trials had quality assessment scores of A.

**NRT (patch, gum, lozenge, sublingual, inhaler, and spray):** Of the 19 trials comparing nicotine patch with placebo, five trials were rated A,<sup>64,68,77,78,80</sup> seven trials were rated B,<sup>61,67,69,72-74,76</sup> six trials were rated C,<sup>58,60,62,65,70,75</sup> and one trial was rated D.<sup>59</sup>

Of the 19 trials comparing nicotine gum with placebo, seven trials were rated A,<sup>81,84,87,91,97,98,100</sup> three trials were rated B,<sup>82,83,103</sup> five trials were rated C,<sup>93,94,99,101,102</sup> three trials were rated D,<sup>85,92,95</sup> and one trial was rated E.<sup>90</sup>

One trial of nicotine lozenge versus placebo,<sup>104</sup> two trials of nicotine sublingual versus placebo,<sup>105,107</sup> five trials of nicotine oral inhaler versus placebo,<sup>108-112</sup> and four trials of nicotine nasal spray versus placebo<sup>113-116</sup> were all rated A.

Two trials<sup>117,118</sup> comparing nicotine patch with nicotine nasal spray and one trial<sup>120</sup> comparing nicotine lozenge with nicotine gum were rated A. One trial<sup>122</sup> of nicotine spray versus nicotine gum versus nicotine inhaler was rated C.

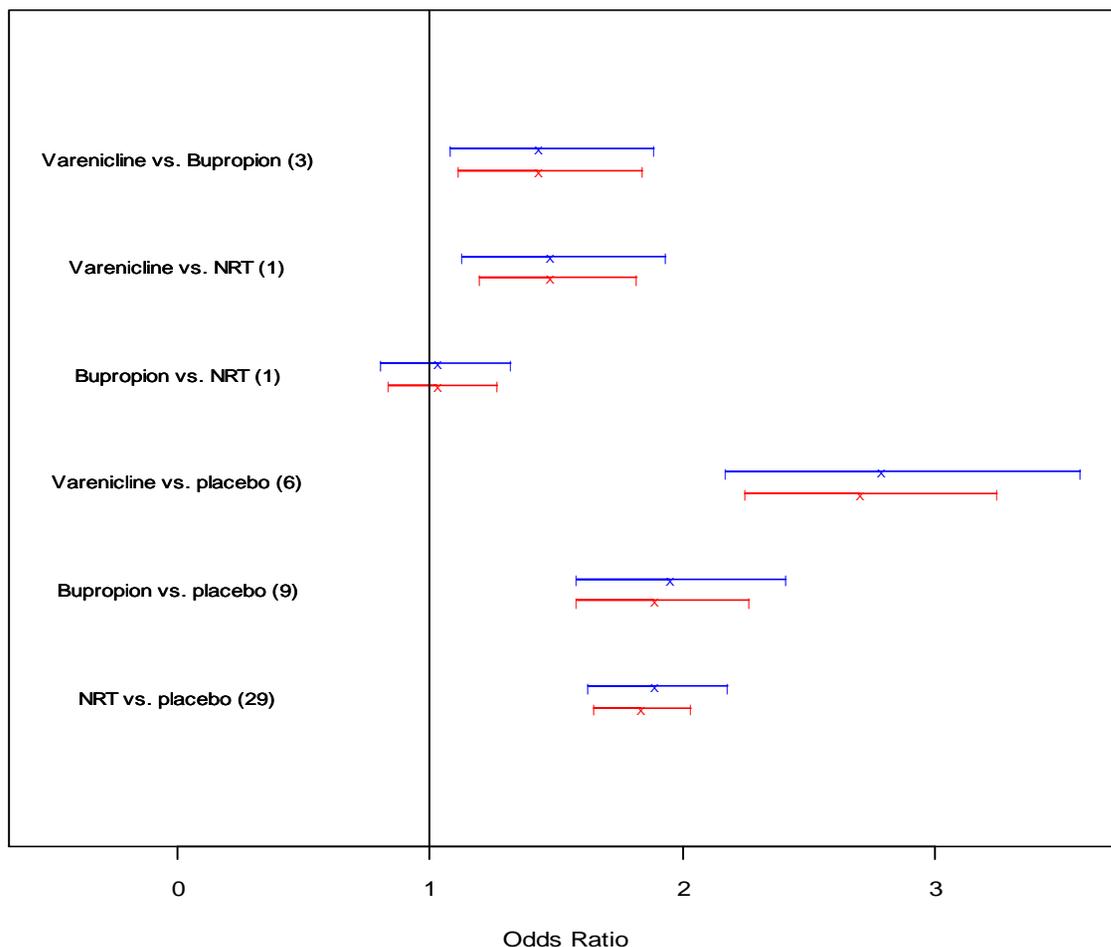
**Bupropion:** Of the 13 trials comparing bupropion with placebo, 12 trials were rated A,<sup>158,159,163,165,167,168,173-176,178,180</sup> and one trial was rated B.<sup>164</sup> One trial<sup>182</sup> comparing bupropion with nicotine patch was rated C.

**Summary of findings**

Pooled estimates were obtained using MTC meta-analysis. Appendix 8a shows the clinical analyses of NRT, bupropion, and varenicline, where NRT represents any nicotine replacement product. In Appendix 8b, the nicotine replacement products were separated and compared with bupropion and varenicline. In Appendix 8c, the nicotine replacement products were compared amongst themselves. The adverse events appear in Appendix 8d.

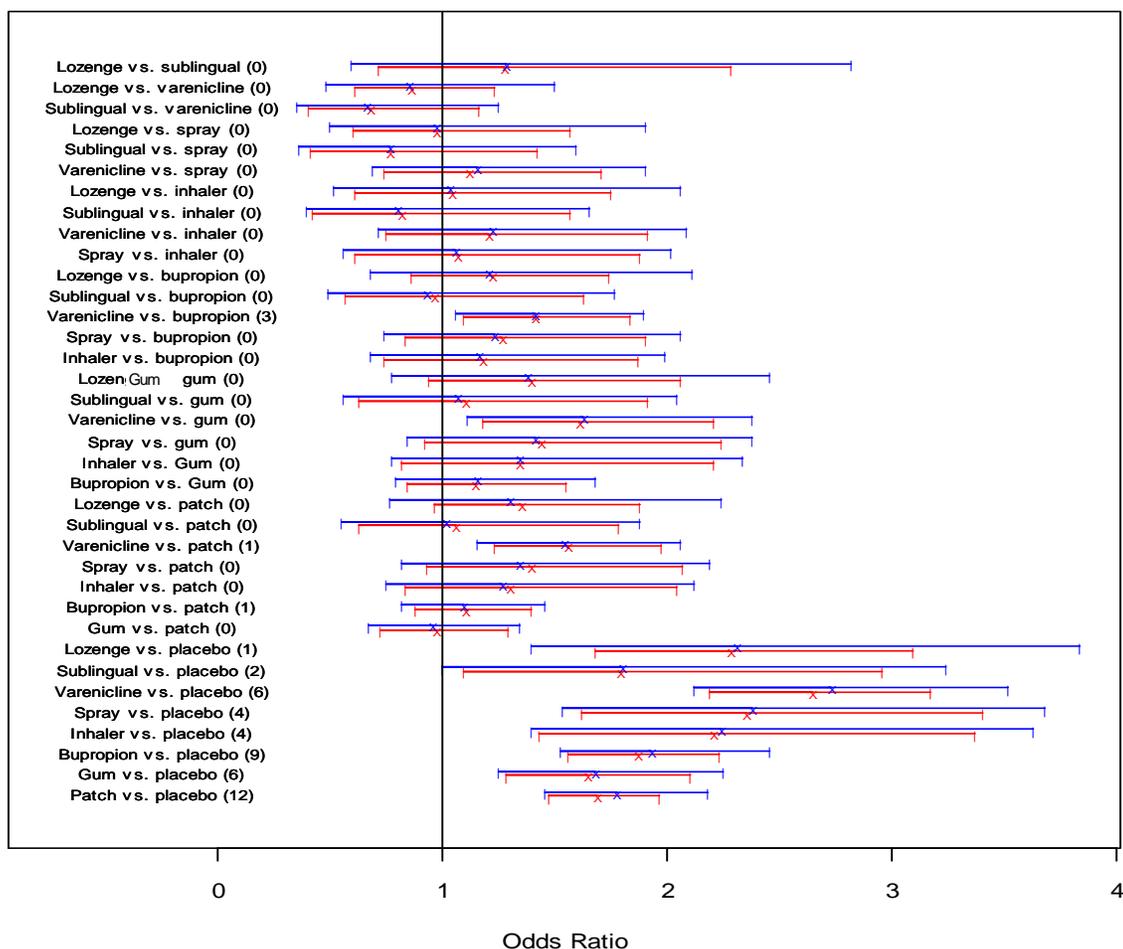
The outcome measures include three types of abstinence rates: continuous abstinence (CAR), prolonged abstinence and point prevalence abstinence (PPA), determined, at a minimum, after six months follow-up. The relapse rates were identified at the one year follow-up point.

**Figure 1:** Continuous Abstinence Rates at One Year — NRT Combined In Analysis



NOTE: Numbers in parentheses indicate the number of trials with direct comparisons. Red (bottom) bars: logistic regression MTC pooled fixed effects (OR, 95% CI). Blue (top) bars: Bayesian MTC pooled random effects (OR, 95% CrI). CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; NRT = nicotine replacement therapy; OR = odds ratio: vs = versus.

**Figure 2: Continuous Abstinence Rates at One Year — NRT Analyzed Separately**



NOTE: Numbers in parentheses indicate the number of trials with direct comparisons. Red (bottom) bars: logistic regression MTC pooled fixed effects (OR, 95% CrI). Blue (top) bars: Bayesian MTC pooled random effects (OR, 95% CrI).  
 CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; NRT = nicotine replacement therapy; OR = odds ratio: vs = versus.

**Continuous abstinence rate:** At six-month and one-year follow-ups, NRT, bupropion, and varenicline were all shown to be clinically efficacious as aids in smoking cessation compared with placebo (Appendix 8a). In representative plots for CAR at one year, all nicotine replacement products were either analyzed together (Figure 1) or separately (Figure 2). No difference between bupropion and NRT was observed. At one year, varenicline was found to be superior to bupropion (OR 1.43, 95% CrI 1.08 to 1.89) and conventional NRT used after quit date (OR 1.47, 95% CrI 1.13 to 1.93), particularly to nicotine gum (OR 1.63, 95% CrI 1.11 to 2.38) and nicotine patch (OR 1.54, 95% CrI 1.15 to 2.06).

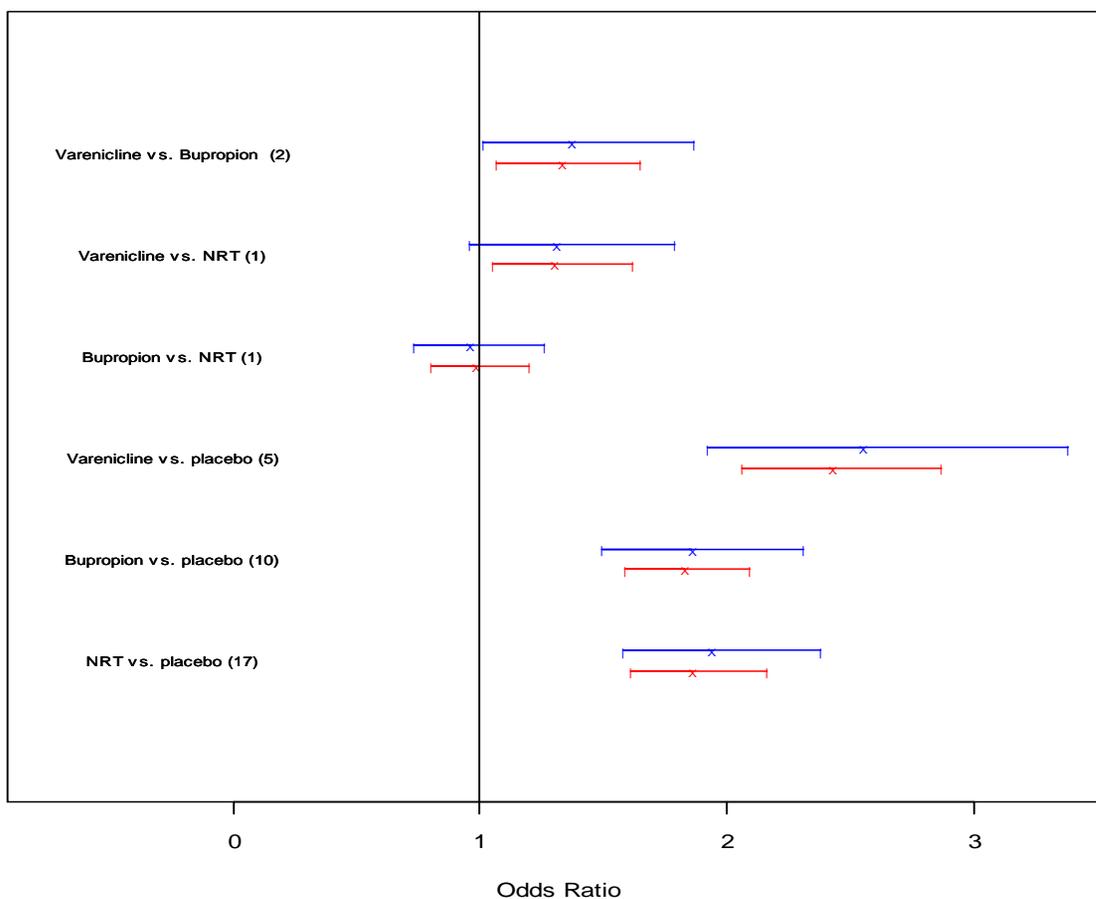
Analyses showed that all nicotine replacement products were efficacious compared with placebo (Appendices 8b and 8c). Nicotine patch retained its clinical efficacy up to seven years of follow-up (OR 4.15, 95% CrI 1.28 to 13.45) in one trial.<sup>77</sup> However, the difference lost statistical significance at 10 years (OR 2.97, 95% CrI 0.94 to 9.43). Nicotine gum, inhaler, and spray

showed no difference at two years of follow-up compared with placebo. The authors of this report could not identify any differences in quit rates among the nicotine products, but wide CIs preclude definitive conclusions. When bupropion was compared with each nicotine replacement product, no differences were observed. At one year, varenicline was found to be better than conventional nicotine patch (OR 1.54, 95% CrI 1.15 to 2.06) and nicotine gum (OR 1.41, 95% CrI 1.06 to 1.89) used after quit date.

***Prolonged abstinence rate:*** At six month and one year follow-ups, when NRTs were compared with each other or with bupropion or varenicline, there were neither differences between drugs and placebo nor between drug classes (Appendices 8b and 8c).

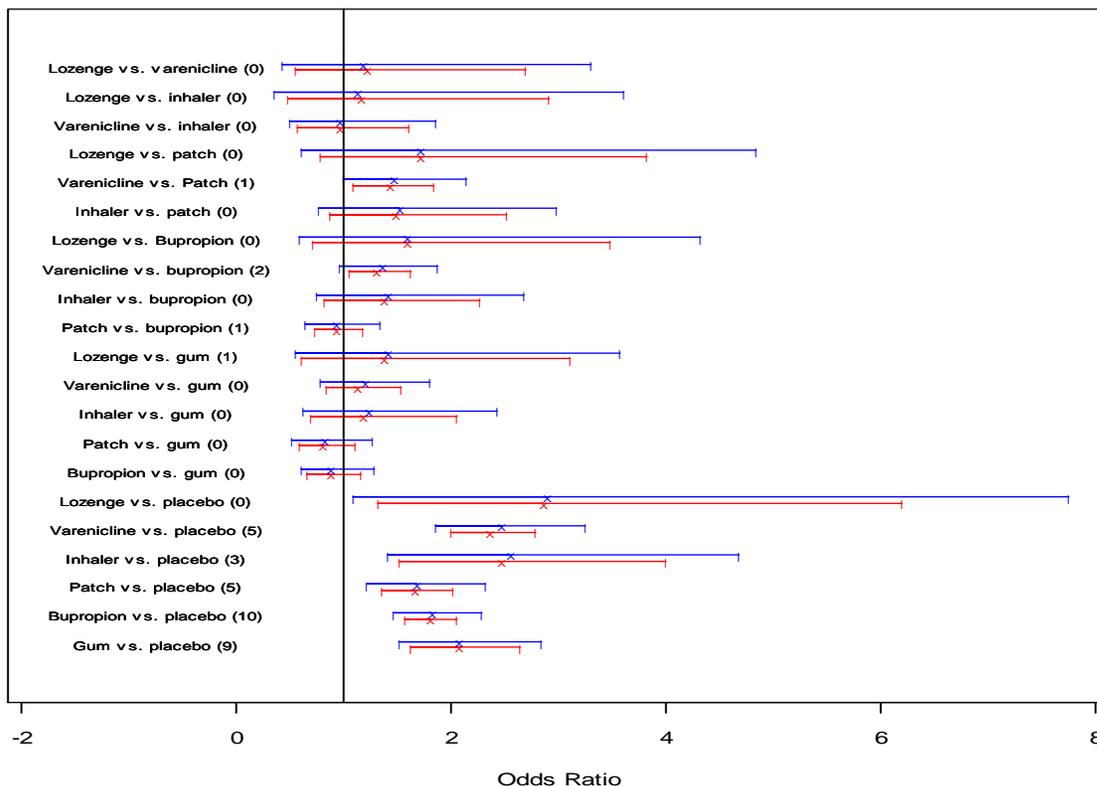
***Point prevalence abstinence rate:*** At one year follow-up, NRT (including patch, gum, inhaler, and lozenge), bupropion, and varenicline were all efficacious as aids for smoking cessation compared with placebo (Appendices 8a and 8b). In the representative plots for PPA at one year, all nicotine replacement products were either analyzed together (Figure 3) or separately (Figure 4). Bupropion showed no significant differences when compared with any nicotine replacement product. Varenicline was found to be superior to bupropion at six months (OR 1.43, 95% CrI 1.15 to 1.79), and borderline at one year (OR 1.35, 95% CrI 0.97 to 1.88). Varenicline was also found to be better than nicotine patch (OR 1.50, 95% CrI 1.15 to 1.96) and nicotine gum (OR 1.63, 95% CrI 1.18 to 2.25) at six months follow-up, but the statistical significance was lost at one year. None of the nicotine replacement products were found to be better than any other.

**Figure 3:** Point Prevalence Abstinence Rates at One Year — NRT Combined In the Analysis



NOTE: Numbers in parentheses indicate the number of trials with direct comparisons. Red (bottom) bars: logistic regression MTC pooled fixed effects (OR, 95% CI). Blue (top) bars: Bayesian MTC pooled random effects (OR, 95% CrI). CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; NRT = nicotine replacement therapy; OR = odds ratio; vs = versus.

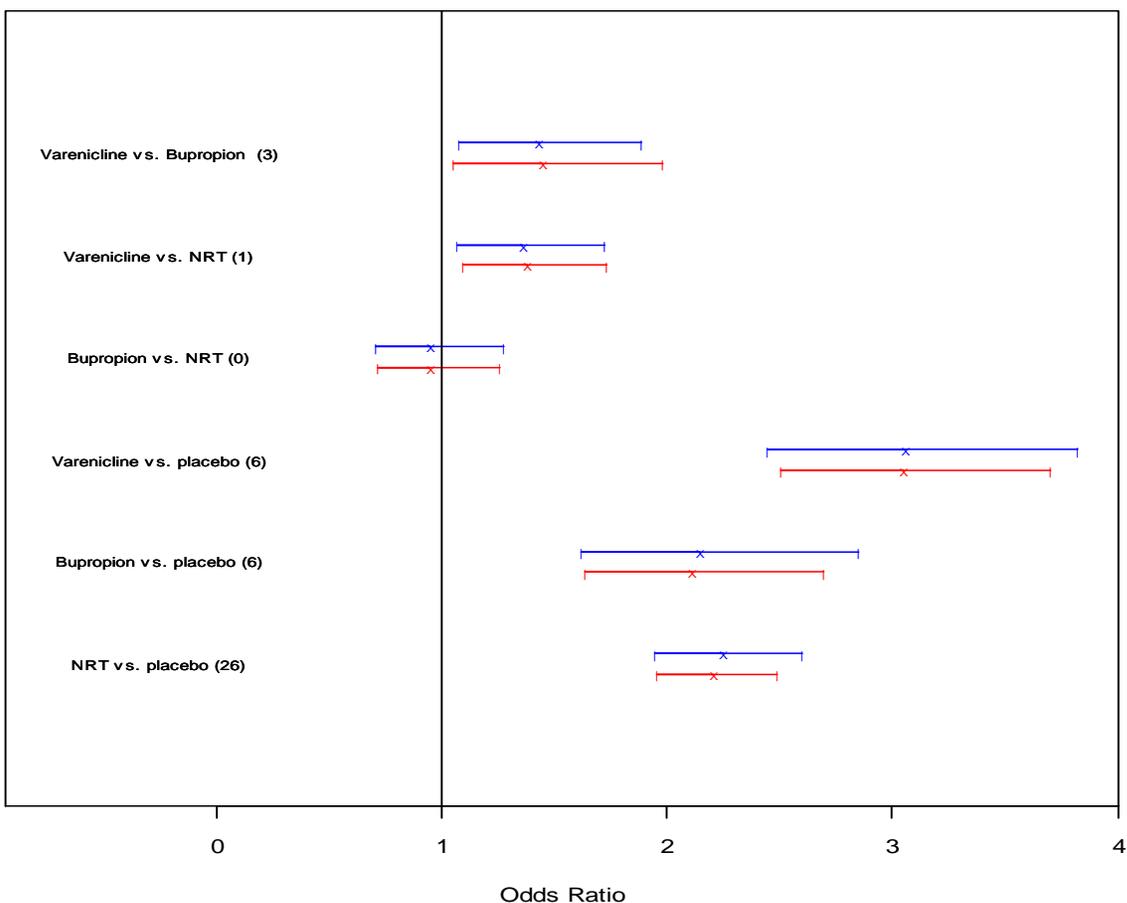
**Figure 4: Point Prevalence Abstinence Rates at One Year — NRT Analyzed Separately**



NOTE: Numbers in parentheses indicate the number of trials with direct comparisons. Red (bottom) bars: logistic regression MTC pooled fixed effects (OR, 95% CI). Blue (top) bars: Bayesian MTC pooled random effects (OR, 95% CrI). CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; NRT = nicotine replacement therapy; OR = odds ratio; vs = versus.

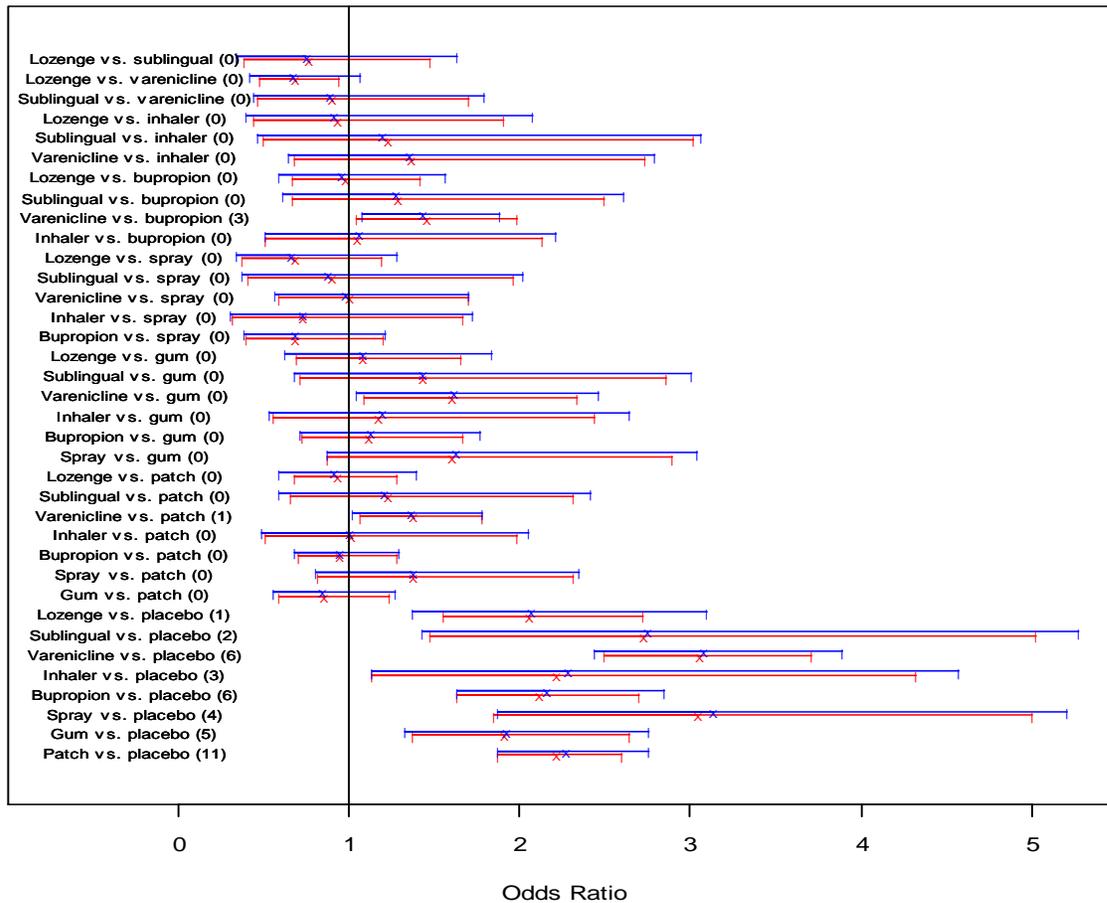
**Relapse:** When the relapse rates were analyzed at one year relative to the quit rates at three months follow-up, all pharmacotherapies including all NRTs, bupropion, and varenicline showed higher relapse rates compared with placebo (Appendix 8a and Figure 5). This might be due to higher quit rates with the drug therapy compared to placebo after three months, and smokers in the placebo group might have relapsed during the first three months. Higher relapse rates were found with varenicline when compared with nicotine patch (OR 1.36, 95% CrI 1.03 to 1.78), nicotine gum (OR 1.61, 95% CrI 1.05 to 2.46), and bupropion (OR 1.43, 95% CrI 1.08 to 1.89) (Appendix 8b and Figure 6). No differences were found between bupropion and each NRT or between NRTs.

**Figure 5: Relapse at One Year — NRT Combined in the Analysis**



NOTE: Numbers in parentheses indicate the number of trials with direct comparisons. Red (bottom) bars: logistic regression MTC pooled fixed effects (OR, 95% CI). Blue (top) bars: Bayesian MTC pooled random effects (OR, 95% CrI). CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; NRT = nicotine replacement therapy; OR = odds ratio; vs = versus.

**Figure 6: Relapse at One Year — NRT Analyzed Separately**



NOTE: Numbers in parentheses indicate the number of trials with direct comparisons. Red (bottom) bars: logistic regression MTC pooled fixed effects (OR, 95% CI). Blue (top) bars: Bayesian MTC pooled random effects (OR, 95% CrI). CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; NRT = nicotine replacement therapy; OR = odds ratio: vs = versus.

**Adverse events:** Appendix 8d shows the estimated effect sizes comparing the interventions of interest for a series of 34 identified adverse events. Only available outcomes data of the interventions were presented.

- *Any adverse events:* All pharmacotherapies, except nicotine inhaler, were associated with higher numbers of adverse events compared with placebo. Nicotine spray seemed to be associated with more adverse events than nicotine patch (OR 3.83, 95% CrI 1.07 to 13.76) or nicotine inhaler (OR 5.12, 95% CrI 1.28 to 20.48).
- *Discontinued because of adverse events:* Nicotine patch, bupropion, and varenicline showed a higher proportion of withdrawals due to adverse events compared with placebo. The pooled ORs (95% CrI) were 1.41 (1.02 to 1.94), 1.74 (1.31 to 2.31), and 1.52 (1.09 to 2.12) respectively.
- *Nonfatal serious adverse events:* Bupropion was associated with higher non-fatal serious adverse events compared with placebo (OR 2.72, 95% CrI 1.24 to 5.96). No definition of serious adverse events was provided in the trials.
- *Hospitalizations:* No difference was found between bupropion and placebo (OR 0.69; 95% CrI 0.06 to 7.44).

- *Influenza*: Varenicline, bupropion, and nicotine patch showed no difference compared with placebo. The ORs (95% CrI) were 1.27 (0.43 to 3.72), 0.74 (0.26 to 2.06), and 0.65 (0.15 to 2.74) respectively.
- *Respiratory tract infection*: No differences were observed when comparing drugs with placebo or active therapies with each other.
- *Headache*: Treatment with varenicline was associated with a higher frequency of headache compared with placebo (OR 1.41, 95% CrI 1.11 to 1.79), bupropion (OR 1.32, 95% CrI 1.01 to 1.72), nicotine patch (OR 1.40, 95% CrI 1.04 to 1.88), and nicotine gum (OR 1.70, 95% CrI 1.08 to 2.69). Other pairwise comparisons were inconclusive.
- *Dizziness*: Treatment with varenicline or bupropion was associated with a higher frequency of dizziness compared with nicotine patch. The ORs of patch versus bupropion and of varenicline versus patch were 0.54 (95% CrI 0.32 to 0.92) and 1.84 (95% CrI 1.08 to 3.13) respectively. Other pairwise comparisons were inconclusive.
- *Gastritis*: One trial of nicotine sublingual versus placebo reported gastritis as an adverse event. The difference was inconclusive (OR, 2.44; 95% CrI 0.89 to 6.72).
- *Nausea or vomiting*: Bupropion, varenicline, nicotine spray, nicotine sublingual, and nicotine lozenge were associated with higher frequencies of nausea or vomiting compared with placebo. Varenicline was found to be worse than bupropion (OR 2.73, 95% CrI 1.94 to 3.84), nicotine patch (OR 3.36, 95% CrI 2.34 to 4.81), nicotine gum (OR 2.63, 95% CrI 1.47 to 4.55), nicotine inhaler (OR 3.13, 95% CrI 1.45 to 6.67), and nicotine spray (OR 2.22, 95% CrI 1.11 to 4.35). Nicotine sublingual was associated with higher rates of nausea or vomiting compared with nicotine patch (OR 3.80, 95% CrI 1.55 to 9.32), nicotine gum (OR 2.95, 95% CrI 1.10 to 7.92), nicotine inhaler (OR 3.50, 95% CrI 1.17 to 10.44), and bupropion (OR 3.09, 95% CrI 1.24 to 7.72). Other pairwise comparisons were inconclusive.
- *Upper abdominal pain*: Differences in pairwise comparisons among placebo, nicotine patch, bupropion, and varenicline were inconclusive.
- *Gastrointestinal disturbance*: Nicotine gum, varenicline, nicotine inhaler, nicotine sublingual, and nicotine lozenge were associated with higher gastrointestinal disturbance compared with placebo. Treatment with nicotine patch was less likely to be associated with gastrointestinal disturbance compared with nicotine gum (OR 0.37, 95% CrI 0.16 to 0.86), nicotine inhaler (OR 0.22, 95% CrI 0.08 to 0.58), and varenicline (OR 0.37, 95% CrI 0.16 to 0.86). Other pairwise comparisons were inconclusive.
- *Constipation or diarrhea*: Compared with placebo or nicotine patch, bupropion and varenicline were associated with higher frequency of constipation or diarrhea. Other pairwise comparisons were inconclusive.
- *Sleep disturbance*: Compared with placebo, nicotine patch, bupropion, and varenicline were associated with more sleep disturbance. No difference was found between nicotine patch, bupropion, or varenicline.
- *Insomnia*: Compared with placebo, bupropion and varenicline were associated with a higher rate of insomnia. Insomnia was also worse with bupropion compared with varenicline (OR 1.61, 95% CrI 1.25 to 2.04) or nicotine patch (OR 1.96, 95% CrI 1.47 to 2.63). No difference was observed between nicotine patch and placebo (OR 1.26, 95% CrI 0.95 to 1.66) or nicotine patch and varenicline (OR 0.81, 95% CrI 0.60 to 1.11).
- *Abnormal dreams*: Compared with placebo, nicotine patch and varenicline were associated with more occurrences of reported abnormal dreams. Occurrences of abnormal dreams were found to be worse with varenicline than bupropion (OR 2.17, 95% CrI 1.09 to 4.35). No

difference was observed between bupropion and placebo (OR 1.45, 95% CrI 0.74 to 2.83), varenicline and nicotine patch (OR 1.06, 95% CrI 0.47 to 2.43), or bupropion and nicotine patch (OR 0.49, 95% CrI 0.21 to 1.14).

- *Anxiety or irritability*: No difference was observed for anxiety or irritability when comparing placebo, bupropion, varenicline, and nicotine patch.
- *Asthenia or fatigue*: Varenicline, bupropion, and nicotine patch showed no difference compared with placebo. Varenicline was associated with a greater risk than nicotine patch (OR 2.28, 95% CrI 1.15 to 5.80).
- *Increased appetite*: Pairwise comparisons among placebo, bupropion, varenicline, and nicotine patch were inconclusive or showed no differences.
- *Allergy*: Pairwise comparisons among placebo, bupropion, varenicline, and nicotine patch were inconclusive.
- *Skin reactions*: Nicotine patch was associated with a higher risk of skin reactions compared with placebo (OR 3.11, 95% CrI 2.47 to 3.93).
- *Sore or irritated throat*: Nicotine spray was associated with a higher risk for causing sore or irritated throat when compared with placebo (OR 10.59, 95% CrI 4.58 to 24.46), nicotine gum (OR 8.07, 95% CrI 2.83 to 23.07), nicotine inhaler (OR 3.07, 95% CrI 1.15 to 8.14), nicotine lozenge (OR 9.09, 95% CrI 1.92 to 50.00), nicotine patch (OR 12.50, 95% CrI 3.45 to 50.00), and bupropion (OR 16.67, 95% CrI 1.92 to 100). Nicotine inhaler was associated with a higher risk of sore and irritated throat compared with placebo (OR 3.45, 95% CrI 1.87 to 6.39), nicotine gum (OR 2.63, 95% CrI 1.07 to 6.47), and bupropion (OR 5.00, 95% CrI 1.19 to 20.00).
- *Dry mouth*: Bupropion was associated with a higher risk of dry mouth when compared with placebo (OR 2.00, 95% CrI 1.58 to 2.52), nicotine patch (OR 2.86, 95% CrI 1.67 to 5.00), and varenicline (OR 1.59, 95% CrI 1.08 to 2.33).
- *Mouth irritation (ulcer or canker sore)*: Pairwise comparisons among placebo, bupropion, nicotine inhaler, nicotine lozenge, and nicotine gum were inconclusive or showed no differences.
- *Oral discomfort or jaw soreness*: Pairwise comparisons among placebo, nicotine gum, nicotine inhaler, and nicotine sublingual were inconclusive or showed no differences.
- *Hiccups*: Nicotine gum, nicotine sublingual, nicotine lozenge, and nicotine inhaler appeared to be associated with more hiccups compared with placebo, although the associated CrIs were wide. The comparisons between interventions were inconclusive.
- *Excessive salivation*: One trial showed no difference between nicotine gum and placebo (OR, 1.42; 95% CrI 0.81 to 2.48).
- *Coughing*: Nicotine inhaler and nicotine spray showed higher risk of coughing compared with placebo and bupropion. The pooled ORs comparing nicotine inhaler versus bupropion and nicotine spray versus bupropion were 7.14 (95% CrI 1.85 to 25.00) and 8.33 (95% CrI 2.08 to 33.33) respectively.
- *Nasal irritation*: No differences were observed in pairwise comparisons of placebo, nicotine spray, and nicotine patch.
- *Runny nose*: Nicotine spray was associated with a higher risk of runny nose compared with placebo (OR 8.05, 95% CrI 1.09 to 59.28).
- *Sneezing*: Nicotine spray was associated with a higher risk of sneezing when compared with placebo (OR 5.77, 95% CrI 2.09 to 15.94).

- *Watery eyes*: Nicotine spray was associated with a higher risk of watery eyes compared with placebo (OR 7.82, 95% CrI 2.04 to 29.90).
- *Blurred vision*: The difference between bupropion and placebo was inconclusive.
- *Irregular heartbeat*: The difference between bupropion and placebo was inconclusive.

## **Combined therapy**

### ***Quality assessment***

One trial<sup>183</sup> of nicotine patch plus nicotine spray versus nicotine patch was rated B. One trial<sup>184</sup> of nicotine inhaler plus nicotine patch versus nicotine inhaler was rated A. One trial<sup>196</sup> of nicotine patch plus nicotine gum versus nicotine patch was rated A. One trial<sup>187</sup> of bupropion plus nicotine gum versus bupropion was rated A. One trial<sup>188</sup> of bupropion plus nicotine patch versus bupropion was rated A. One trial<sup>193</sup> of nicotine patch plus bupropion versus nicotine patch was rated A.

### ***Summary of findings***

The results were summarized using a qualitative approach.

***Nicotine patch plus nicotine spray versus nicotine patch***: Blondal et al. (1999)<sup>183</sup> evaluated the efficacy of using nicotine patch for five months plus nicotine nasal spray for one year. The comparator was nicotine patch and placebo spray. Adding active nicotine nasal spray to nicotine patch increased the CAR at six months (31.4% versus 16.0%; OR 2.40; 95% CI 1.27 to 4.50) and one year (27.1% versus 10.9%; OR 3.03; 95% CI 1.51 to 6.14). The relapse rates at one year relative to the quit rates after three months were 27.3% and 56.7% for the combined and monotherapy groups respectively. The abstinence rate remained high with the combined therapy at six years, but the difference lost statistical significance (16.2% versus 8.5%; OR, 2.09; 95% CI 0.93 to 4.72).

***Nicotine inhaler plus nicotine patch versus nicotine inhaler***: Bohadana et al. (2000)<sup>184</sup> found no difference between treatment groups (nicotine inhaler plus nicotine patch versus nicotine inhaler versus placebo patch) in long-term CAR at six months (25.0% versus 22.5%; OR 1.15; 95% CI 0.72 to 1.82), or at one year (19.5% versus 14.0%; OR 1.49; 95% CI 0.88 to 2.53). The relapse rates at one year relative to the quit rates after three months were similar in both groups (54% versus 55%).

***Nicotine patch plus nicotine gum versus nicotine patch***: Kornitzer et al. (1995)<sup>185</sup> found that the CAR at six months was superior in the group who was treated with nicotine patch plus nicotine gum as compared with the group who was treated with nicotine patch plus placebo gum (27.5% versus 15.3%; OR 2.10; 95% CI 1.18 to 3.71). However, the superiority in the abstinence of the combined therapy lost due to wider CIs at one-year follow-up (18.1% versus 12.7%; OR 1.53; 95% CI 0.81 to 2.88). The relapse rates at one year relative to the quit rates after three months were similar for both groups (47% versus 44%).

***Bupropion plus nicotine gum versus bupropion***: Piper et al. (2007)<sup>187</sup> found that adding active nicotine gum to bupropion did not increase abstinence compared with bupropion and placebo gum. The seven-day PPA rates at six months were 22.8% and 24.6% (OR 0.91; 95% CI 0.59 to 1.40), and at one year were 20.6% and 18.8% (OR 1.13; 95% CI 0.71 to 1.79) for bupropion plus nicotine gum and bupropion plus placebo gum, respectively.

**Bupropion plus nicotine patch versus bupropion:** Jorenby et al. (1999)<sup>188</sup> found that the abstinence rates were higher with bupropion plus nicotine patch compared with bupropion alone, but differences were felt in wide CIs. The seven-day PPA rates for both treatment groups were 38.8% versus 34.8% (OR 1.18; 95% CI 0.82 to 1.71) at six months and 35.5% versus 30.3% (OR 1.26; 95% CI 0.87 to 1.85) at one year. The one-year CARs were 22.5% and 18.4% (OR 1.28; 95% CI 0.82 to 1.99) for the combination and monotherapy groups, respectively.

**Nicotine patch plus bupropion versus nicotine patch:** Simon et al. (2004)<sup>193</sup> found that adding active bupropion to nicotine patch treatment did not improve the abstinence rates at six months or one year compared with placebo bupropion and nicotine patch. The CARs that were assessed at one year of follow-up were 15% in the nicotine patch plus bupropion group and 19% in the nicotine patch plus placebo bupropion group (OR 0.76; 95% CI 0.39 to 1.49). Similar results were observed for the seven-day PPA rates (19% versus 23.6%; OR 0.76; 95% CI 0.41 to 1.41) at one year.

**Nicotine patch plus nicotine lozenge versus bupropion plus nicotine lozenge versus monotherapies:** Piper et al. (2009)<sup>46</sup> found that the ORs (95% CI) at six months post-quit were 1.63 (1.06 to 2.51) for bupropion, 1.76 (1.15 to 2.70) for nicotine lozenge, 1.83 (1.20 to 2.81) for nicotine patch, 1.74 (1.13 to 2.67) for bupropion plus lozenge, and 2.34 (1.54 to 3.57) for patch plus lozenge, relative to placebo. Relative to monotherapies, patch plus lozenge provided higher six-month abstinence rates (OR 1.35; 95% CI 1.01 to 1.79).

**b) Among the general population of smokers using varenicline or bupropion or NRT, what is the clinical effectiveness of adding a behavioural support program to drug therapy?**

## **NRT versus NRT plus behavioural support**

### **Quality assessment**

Of the three trials<sup>123,125,126</sup> of nicotine patch versus nicotine patch plus behavioural support, two were rated B<sup>123,125</sup> and one was rated C.<sup>126</sup>

Of the five trials<sup>85,131-134</sup> comparing nicotine gum with nicotine gum plus behavioural support, one was rated B,<sup>131</sup> one was rated C,<sup>134</sup> and three were rated D.<sup>85,132,133</sup>

### **Summary of findings**

**Nicotine patch versus nicotine patch plus behavioural support:** Adding behavioural support to nicotine patch produced no difference in CAR or PPA rates compared with nicotine patch at six months or one year of follow-up (Appendix 8e). The ORs for six-month CAR and one-year CAR were 1.16 (95% CrI 0.69 to 1.96) and 0.96 (95% CrI 0.54 to 1.70), respectively. The ORs for six-month PPA and one-year PPA were 1.61 (95% CrI 0.61 to 4.20) and 1.44 (95% CrI 0.50 to 4.19), respectively.

**Nicotine gum versus nicotine gum plus behavioural support:** Adding behavioural support to nicotine gum produced no difference in point prevalence rates when compared with nicotine gum at six months or one year of follow-up (Appendix 8e). The ORs for six-month PPA and one-year PPA were 1.13 (95% CrI 0.53 to 2.43) and 1.02 (95% CrI 0.48 to 2.18), respectively.

## **NRT plus behavioural support versus control (usual care)**

### ***Quality assessment***

One trial<sup>143</sup> of nicotine patch plus minimal structured counselling versus non-treated control was rated B.

### ***Summary of findings***

Rodríguez-Artalejo et al. (2003)<sup>143</sup> compared the effect of minimal structured counselling and nicotine patch (intervention) with standard clinical practice (control) on smoking cessation in the workplace. The CAR at 12 months was 20.2% for the intervention versus 8.7% for the control group (OR, 2.58; 95% CI 1.13 to 5.80).

## **NRT plus behavioural support versus behavioural support**

### ***Quality assessment***

Of the nine trials<sup>145-147,149,150,152,154,156,157</sup> of NRT plus behavioural support versus behavioural support alone, five were rated B,<sup>149,150,152,156,157</sup> three were rated C,<sup>145,146,154</sup> and one was rated D.<sup>147</sup>

### ***Summary of findings***

The ORs of CARs or PPA rates at six months or at one year of follow-up were greater than 1, indicating a trend that the addition of nicotine patch or nicotine gum to behavioural support was better than behavioural support alone (Appendix 8e, Behaviour ± NRT). However, the 95% CrIs were wide and covered the middle neutral point of 1.

## **Bupropion versus bupropion plus behavioural support**

### ***Quality assessment***

One trial<sup>168</sup> comparing bupropion with bupropion plus brief individual counselling was rated A.

### ***Summary of findings***

McCarthy et al. (2008)<sup>168</sup> found that the addition of counselling did not increase the overall abstinence rates resulting from the use of bupropion. A comparison of bupropion plus counselling with bupropion alone showed no significant differences in PPA (18.6% versus 13.8%; OR 1.43, 95% CI 0.70 to 2.90) or prolonged abstinence (30.1% versus 25.0%; OR 1.29, 95% CI 0.72 to 2.31) at six months post-quit. Similar results were found at one-year follow-up for PPA (21.1% versus 20.7%; OR 1.03, 95% CI 0.55 to 1.95) or prolonged abstinence (20.4% versus 18.1%; OR 1.16, 95% CI 0.60 to 2.23).

## **c) What is the impact of “free” or “paid-for” pharmacotherapy on the clinical effectiveness of drugs used for smoking cessation therapy?**

### ***Quality assessment***

One trial<sup>62</sup> comparing the efficacy of no-pay versus pay-for over-the-counter nicotine patch to be used in smoking cessation was rated C. One trial<sup>195</sup> examining the effects of financial reimbursement for all smoking cessation treatments — including bupropion, NRT, and behavioural counselling — compared with no reimbursement was rated A. One trial<sup>194</sup> assessing the financial incentives for smoking cessation among employees of a multinational company that was based in the US was rated A.

## Summary of findings

The results were summarized using a qualitative approach.

Hays et al. (1999)<sup>62</sup> assessed the effect of free nicotine patch (no-pay) and patch that was bought over the counter (pay) on smoking abstinence. The seven-day PPA at six-month follow-up was 10.8% in the -pay group and 8.7% in the no pay group (OR 1.30, 95% CI 0.70 to 2.20). No difference was observed.

Kaper et al. (2005)<sup>195</sup> examined the effects of financial reimbursement (no-pay) for all smoking cessation treatments that had been shown to be efficacious and were available in The Netherlands. Smokers in the control group (pay) paid for the treatment. The seven-day PPA rate at six-month follow-up was 5.5% for the no-pay group and 2.8% for the pay group (OR 2.30, 95% CI 1.2 to 4.1). A difference was observed.

Volpp et al. (2009)<sup>194</sup> assessed the financial incentives for smoking cessation among employees of a multinational company that was based in the US. The incentive group had higher CARs than the information-only group at six-month (14.7% versus 5%; OR 3.28; 95% CI 1.98 to 5.44) or one-year (9.4% versus 3.6%; OR 2.76; 95% CI 1.53 to 5.00) follow-up.

**d) Among smokers, what is the clinical effectiveness of treating specific populations (adolescents, pregnant women, and those with underlying diseases) with varenicline or bupropion or NRT, including a combination of these agents, with behavioural support programs?**

### Adolescents

#### Quality assessment

One trial<sup>119</sup> of nicotine patch versus nicotine gum versus placebo was rated C, and one trial<sup>192</sup> of NRT plus bupropion versus NRT was rated A.

#### Summary of findings

The results were summarized using a qualitative approach.

**Nicotine patch versus nicotine gum versus placebo:** Moolchan et al. (2005)<sup>119</sup> found the PPA rates at six months were 20.6% for nicotine patch, 8.7% for nicotine gum, and 5% for placebo. The OR (95% CI) in nicotine patch to placebo comparison was 4.93 (0.95 to 25.57); the OR (95% CI) in nicotine gum to placebo comparison was 1.81 (0.31 to 10.45); and the OR in nicotine patch to nicotine gum comparison was 2.72 (0.73 to 10.19).

**Combined therapy (NRT plus bupropion) versus NRT:** Killen et al. (2004)<sup>192</sup> randomized adolescent smokers to receive nicotine patch plus bupropion or nicotine patch plus placebo. There was no difference in the seven-day PPA between treatment groups (8% versus 7%; OR 1.05; 95% CI 0.38 to 2.92) at six-month follow-up.

### Substance abuse (alcohol, methadone)

#### Quality assessment

Of the four trials,<sup>63,129,139,148</sup> one<sup>63</sup> comparing nicotine patch with placebo in smokers with a history of alcoholism was rated C. One trial<sup>129</sup> comparing nicotine patch with nicotine patch plus

behavioural support in methadone-maintained smokers was rated A. One trial<sup>139</sup> comparing NRT plus behavioural support with control (usual care) among smokers with substance abuse was rated A. One trial<sup>148</sup> comparing NRT plus behavioural support with behavioural support in recovering patients with alcoholism was rated B.

### **Summary of findings**

**Nicotine patch versus placebo:** Hughes et al. (2003)<sup>63</sup> found that the CARs in smokers with a history of alcohol dependence was higher in the active group than the placebo group at six-month follow-up (24% versus 6%; OR 4.90; 95% CI 1.51 to 20.38).

**Nicotine patch plus nicotine gum versus nicotine patch plus placebo gum:** Cooney et al. (2009)<sup>186</sup> reported that the prolonged abstinence rates in alcohol-dependent smokers were higher in the group using nicotine gum compared with the group using placebo gum. The difference was not apparent until the 12-month follow-up period (13% versus 0%, OR 11.00; 95% CI 0.58 to 207.16), but the CI was wide.

**Nicotine patch versus nicotine patch plus behavioural support:** Stein et al. (2006)<sup>129</sup> found no difference in seven-day PPA between treatment groups at six-month follow-up (4.7% versus 5.2%, OR 0.89; 95% CI 0.35 to 2.24) among methadone-maintained smokers.

**NRT plus behavioural support versus control (usual care):** Reid et al. (2008)<sup>139</sup> found no difference in seven-day PPA between intervention and control groups at six-month follow-up (5.7% versus 5.2%; OR 1.06; 95% CI 0.32 to 3.57) among smokers with substance abuse (methadone-maintained, drug, or alcohol-dependent).

**NRT plus behavioural support versus behavioural support:** Martin et al. (1997)<sup>148</sup> found that the PPA rates among smokers who had recovered from alcohol dependence were not different between the intervention (nicotine gum plus behaviour support) and control (behaviour support) groups at six-month follow-up (27% versus 25%; OR 1.09; 95% CI 0.56 to 2.13), or one-year follow-up (27% versus 26%; OR 1.05; 95% CI 0.54 to 2.05).

## **Mental disorder**

### **Quality assessment**

Of the six trials<sup>135,160-162,190,191</sup> on patients with a psychotic disorder, including schizophrenia, one<sup>135</sup> comparing NRT plus behavioural support versus usual care among patients with a psychotic disorder was rated B. Of the three trials<sup>160-162</sup> comparing bupropion versus placebo among patients with schizophrenia, one was rated B,<sup>162</sup> and two were rated C.<sup>160,161</sup> Two trials<sup>190,191</sup> comparing NRT plus bupropion versus NRT among patients with schizophrenia were rated B<sup>191</sup> and C.<sup>190</sup>

### **Summary of findings**

The results were summarized using a qualitative approach.

**NRT plus behavioural support versus usual care:** Baker et al. (2006)<sup>135</sup> found no overall differences comparing the nicotine patch plus behavioural support group to the usual care group in seven-day PPA and CARs that were measured at six-month (9.5% versus 4% [OR 2.54; 95% CI 0.95 to 6.81] and 5.4% versus 2% [OR 2.84; 95% CI 0.74 to 10.92]) and 12-month (10.9%

versus 9.6% [OR 1.72; 95% CI 0.75 to 3.93] and 3.4% versus 0.7% [OR 5.28; 95% CI 0.61 to 45.76]) follow-up.

**Bupropion versus placebo:** Three trials were conducted on small numbers of patients with schizophrenia (18,<sup>160</sup> 53<sup>161</sup> and 32<sup>162</sup> patient groups). At six-month follow-up, the seven-day PPA rates were not different between groups: Evins et al. (2004)<sup>160</sup> (bupropion: 1/9 versus placebo: 0/9; OR 3.35; 95% CI 0.12 to 93.83); Evins et al. (2005)<sup>161</sup> (bupropion: 1/25 versus placebo: 1/28; OR 1.13; 95% CI 0.07 to 18.98); George et al. (2002)<sup>162</sup> (bupropion: 3/16 versus placebo: 1/16; OR 3.46; 95% CI 0.32 to 37.47).

The pooled estimate of PPA rate at six-month follow-up yielded an inconclusive CI (OR 3.95, 95% CrI 0.35 to 44.48) (Appendix 8f).

**Combined therapy (NRT plus bupropion) versus NRT:** Evins et al. (2007)<sup>191</sup> and George et al. (2008)<sup>190</sup> examined the effect of adding bupropion to nicotine patch versus nicotine patch alone in totals of 51 and 58 patients with schizophrenia, respectively. Evins et al. (2007)<sup>191</sup> found that the CARs did not differ by treatment groups at week 24 (patch plus bupropion 5/25 [20%] versus patch 2/26 [8%]; OR 3.00; 95% CI 0.52 to 17.16), or week 52 (patch plus bupropion 3/25 [12%] versus patch 2/26 [8%]; OR 1.64; 95% CI 0.25 to 10.73). Both groups had similar relapse rates at one year (66.7% versus 60%) compared to quit rates at three months. George et al. (2008)<sup>190</sup> also found no difference between treatment groups (patch plus bupropion 4/29 [13.8%] versus patch 0/29 [0.0%], OR 10.41; 95% CI 0.53 to 202.83) achieving seven-day PPA at six months.

## Depression

### Quality assessment

Two trials comparing nicotine gum with placebo among smokers with depression were rated B<sup>88</sup> and D.<sup>86</sup> One trial comparing bupropion, nicotine patch, and placebo was rated A.<sup>188,197</sup>

### Summary of findings

The results were summarized using a qualitative approach.

**Nicotine gum versus placebo:** Hall et al. (1996)<sup>86</sup> found no difference between nicotine gum and placebo in the seven-day PPA at six months (22% versus 33%; OR 0.56; 95% CI 0.14 to 2.13) and at one year (22% versus 33%; OR 0.56; 95% CI 0.14 to 2.13) among smokers with a history of major depressive disorder. In contrast, Kinnunen et al. (2008)<sup>88</sup> showed that the one-year CAR in patients who were depressed was higher with the use of nicotine gum than with the use of placebo (15.1% versus 5.7%; OR 2.93; 95% CI 0.96 to 8.99).

**Bupropion versus nicotine patch versus placebo:** The analysis of data from the trial by Jorenby et al. (1999)<sup>188</sup> and its follow-up study on subjects with history of depression<sup>197</sup> did not show any difference in one-year PPA between bupropion and placebo (OR 4.55, 95% CrI 0.44 to 47.51) or between bupropion and nicotine patch (OR 6.89, 95% CrI 0.77 to 61.68) (Appendix 8f).

## Posttraumatic stress disorder

### Quality assessment

One trial<sup>166</sup> comparing bupropion with placebo in patients with chronic posttraumatic stress disorder was rated C.

### **Summary of findings**

The results were summarized using a qualitative approach.

**Bupropion versus placebo:** The trial by Hertzberg et al. (2001)<sup>166</sup> was conducted on a small number of patients with chronic posttraumatic stress disorder (10 on bupropion and five on placebo). At six-month follow-up, the seven-day PPA rate was 40% (4/10) in bupropion and 20% in placebo (1/5). The OR (95% CI) was 2.67 (0.21 to 33.49).

### **Pregnant women**

#### **Quality assessment**

Of the three trials of pharmacotherapy for smoking cessation among pregnant smokers,<sup>79,89,153</sup> one<sup>79</sup> comparing nicotine patch with placebo was rated C, one<sup>89</sup> comparing nicotine gum with placebo was rated A, and one<sup>153</sup> comparing NRT plus behavioural support with behavioural support alone was rated A.

### **Summary of findings**

The results were summarized using a qualitative approach.

**Nicotine patch versus placebo:** Wisborg et al. (2000)<sup>79</sup> found no difference between groups in CAR at one year after delivery (nicotine patch 15%; placebo 14%; OR 1.09; 95% CI 0.54 to 2.18). There was also no difference in the one-year relapse rate between groups (nicotine patch 27%; placebo 22%).

**Nicotine gum versus placebo:** Oncken et al. (2008)<sup>89</sup> found that the seven-day PPA rates were not different between groups at all follow-up visits, including those six to 12 weeks after delivery (nicotine gum: 11.0%; placebo: 9.6%; OR 1.17; 95% CI 0.46 to 2.96).

**NRT plus behavioural support versus behavioural support:** Pollak et al. (2007)<sup>153</sup> showed that at six months after randomization or three months postpartum, there were no differences between groups in seven-day PPA (intervention 17%; control 14%; OR 1.33; 95% CI 0.55 to 3.20) or CAR (intervention 5%; control 5%; OR 0.97; 95% CI 0.23 to 4.00).

### **Cardiovascular or other smoking-related diseases**

#### **Quality assessment**

Of five trials<sup>96,121,130,179,189</sup> on cardiovascular or other smoking-related diseases, one<sup>96</sup> comparing nicotine gum with placebo in smokers with smoking-related disorders was rated C. One trial<sup>121</sup> comparing nicotine patch, nicotine inhaler, or the combination of patch and inhaler to placebo in smokers who were referred to a lung clinic was rated A. One trial<sup>130</sup> comparing nicotine patch with nicotine patch plus behavioural support in cardiovascular outpatients was rated A. One trial<sup>179</sup> comparing bupropion with placebo in smokers with cardiovascular disease was rated A. One trial<sup>189</sup> of nicotine patch plus nicotine inhaler plus bupropion compared with nicotine patch in medically ill smokers was rated A.

A trial comparing the efficacy and safety of varenicline with that of placebo was identified while this report was being reviewed. The quality of the trial was not assessed, but its results are summarized in this report.

### **Summary of findings**

The results were summarized using a qualitative approach.

**Nicotine gum versus placebo:** Hjalmarson (1984)<sup>96</sup> found that CARs were higher in the nicotine gum group than in the placebo group at six months (37% versus 20%; OR 2.30; 95% CI 1.22 to 4.32) and one year (29% versus 16%; OR 2.14; 95% CI 1.09 to 4.23). The relapse rates at one year compared to quit rates at three months were not different between study groups (45% versus 47%).

**Placebo versus nicotine patch versus nicotine inhaler versus patch plus inhaler:** Tønnesen and Mikkelsen (2000)<sup>121</sup> showed that the nicotine patch maintained superiority in the CARs compared with the placebo at up to 12 months (8.7% versus 1.8%; OR 5.07; 95% CI 1.07 to 24.04). Similar results were observed for PPA at six, nine, and 12 months. No differences were found between nicotine patch, nicotine inhaler, or patch plus inhaler.

**Nicotine patch versus nicotine patch plus behavioural support:** Wiggers et al. (2006)<sup>130</sup> found no differences between groups in PPA at one year (patch 24% versus patch plus behavioural intervention 28%; OR 0.83; 95% CI 0.48 to 1.44).

**Bupropion versus placebo:** Tonstad et al. (2003)<sup>179</sup> showed higher cessation rates for bupropion versus placebo in six-month CAR (27% versus 11%; OR 3.06; 95% CI 1.98 to 4.72); one-year CAR (22% versus 9%; OR 2.88; 95% CI 1.80 to 4.61); six-month PPA (34% versus 12%; OR 3.71; 95% CI 2.45 to 5.60); and one-year PPA (27% versus 12%; OR 2.70; 95% CI 1.77 to 4.11).

**Combined therapy (nicotine patch plus nicotine inhaler plus bupropion) versus nicotine patch:** Steinberg et al. (2009)<sup>189</sup> showed that PPA rates at six months were higher in the combination group (35%) than in the patch group (19%; OR 2.33; 95% CI 1.03 to 5.25).

**Varenicline versus placebo:** Rigotti et al. (2010)<sup>53</sup> showed that the CAR in weeks 9 through 52 was higher for varenicline than placebo (19.2% versus 7.2%; OR 3.14, 95% CI 1.93 to 5.11). Compared with placebo, varenicline did not differ in cardiovascular mortality (0.3% versus 0.6%), all-cause mortality (0.6% versus 1.4%), cardiovascular events (7.1% versus 5.7%), or serious adverse events (6.5% versus 6.0%).

### **Chronic obstructive pulmonary diseases**

#### **Quality assessment**

Among three trials<sup>106,171,177</sup> of pharmacotherapy for smoking cessation in patients with COPD, one<sup>106</sup> comparing nicotine sublingual tablets with placebo was rated A. Two trials<sup>171,177</sup> comparing bupropion with placebo were rated A.

### **Summary of findings**

The results were summarized using a qualitative approach.

**Nicotine sublingual versus placebo:** Tonnesen et al. (2006)<sup>106</sup> found that smoking cessation rates were higher with nicotine sublingual versus placebo in six-month PPA 23.2% versus 9.7%; one-year PPA 17.3% versus 9.7%; and one-year CAR 14.1% versus 5.4%. The OR of one-year

CAR was 2.86 (95% CrI 1.32 to 6.22), and the OR of one-year PPA was 1.94 (95% CrI 1.03 to 3.64) (Appendix 8f).

***Bupropion versus placebo:*** The abstinence rates of both trials<sup>171,177</sup> were higher in the bupropion groups than in the placebo groups. Tashkin et al. (2001)<sup>171</sup> found that the cessation rates with the use of bupropion were superior to those with the use of placebo in six-month CAR (16% versus 9%; OR 1.88; 95% CI 1.02 to 3.48) and six-month PPA (23% versus 16%; OR 1.57; 95% CI 0.95 to 2.59). Wagena et al. (2005)<sup>177</sup> showed similar results in six-month CAR (27.9% versus 14.6%; OR 2.26; 95% CI 1.07 to 4.81), and six-month PPA (30.2% versus 19.1%; OR 1.84; 95% CI 0.91 to 3.70). The pooled estimates were not presented because of population heterogeneity.

## **Hospitalized patients**

### ***Quality assessment***

Among 13 trials<sup>66,66,71,127,136,138,140-142,142,155,170,172</sup> using pharmacotherapy for smoking cessation in hospitalized patients, two<sup>66,71</sup> comparing nicotine patch with placebo were rated A<sup>66</sup> and C.<sup>71</sup> One trial<sup>127</sup> comparing nicotine patch with nicotine patch plus behavioural support was rated A. Of six trials<sup>66,136,138,140-142</sup> comparing NRT plus behavioural support versus usual care in hospitalized patients, three were rated A,<sup>66,138,142</sup> two were rated B,<sup>136,141</sup> and one was rated C.<sup>140</sup> Of two trials comparing NRT plus behavioural support with behavioural support alone, one was rated A<sup>142</sup> and the other was rated B.<sup>155</sup> Two trials<sup>170,172</sup> comparing bupropion versus placebo in hospitalized smokers were both rated A.

### ***Summary of findings***

The results were summarized using a qualitative approach.

***Nicotine patch versus placebo:*** Campbell et al. (1996)<sup>71</sup> randomized hospital inpatients and outpatients with smoking-related respiratory or cardiovascular disease to nicotine patch (N = 115) and placebo (N = 119) groups. All participants received repeated advice and encouragement from counsellors initially and at two, four, eight, and 12 weeks. There was no difference in one-year CARs between nicotine patch and placebo (21% versus 14%; OR 1.58; 95% CI 0.80 to 3.13). The relapse rates for nicotine patch and placebo at one year relative to those who quit smoking at three months were 35% and 43% respectively.

Lewis et al. (1998)<sup>66</sup> randomized hospitalized smokers to nicotine patch (N = 62) and placebo (N = 62) groups. All received pamphlets and counselling on smoking cessation from the physician at initial visits and from the nurse by telephone at one, three, six, and 24 weeks after the initiation of patch treatment. At six-month follow-up, seven-day PPA rates for the nicotine patch and placebo were 9.7% and 6.5% respectively. The OR (95% CI) was 1.55 (0.42 to 5.80).

***Nicotine patch versus nicotine patch plus behavioural support:*** Simon et al. (2003)<sup>127</sup> studied the effect of nicotine patch plus minimal counselling compared with nicotine patch plus intense counselling for smoking cessation in hospitalized patients. The intense counselling included intense cognitive behavioural intervention on the nearest weekday before discharge, in a session lasting 30 to 60 minutes, and five follow-up telephone counselling calls at one and three weeks after discharge and then monthly for the next three months. At one-year follow-up, the biochemically validated seven-day PPA rates were 9% in the minimal counselling group and 16% in the intense intervention group. The OR (95% CI) was 0.55 (0.24 to 1.29).

***NRT plus behavioural support versus usual care:*** There was substantial heterogeneity in the type of behavioural support between studies. Lacasse et al. (2008)<sup>141</sup> used education and psychological support among participants who were given a quit-smoking message from the treating physician, self-help motivational quitting or relapse prevention materials, brief cessation counselling, and follow-up support. Lewis et al. (1998)<sup>66</sup> used a counselling approach with a physician-delivered motivational message to stop smoking, followed by brief telephone counselling from the study nurse at follow-ups after the initiation of patch treatment. Mohiuddin et al. (2007)<sup>138</sup> added weekly individual counselling (approximately 60 minutes per session), for a minimum of three months, to pharmacological treatment. Molyneux et al. (2003)<sup>142</sup> added 20 minutes of counselling on smoking cessation by a doctor or nurse, and an advice leaflet to the intervention group. Nagle et al. (2005)<sup>136</sup> used a nurse-provided intervention in which participants received two brief counselling sessions about withdrawal symptoms, information booklets, and a discharge letter that was addressed to the patient's general practitioner. Simon et al. (1997)<sup>140</sup> used behavioural self-management in which participants received face-to-face in-hospital counselling, an opportunity to view a smoking cessation videotape, self-help literature, and three months of telephone follow-up.

The effect sizes of the trials were not pooled because of the heterogeneous interventions. Three trials<sup>66,136,141</sup> showed no difference in abstinence, and three<sup>138,140,142</sup> showed a difference in abstinence between study groups. Lacasse et al. (2008)<sup>141</sup> found no difference between study groups in the one-year PPA (intervention: 15.2%; control: 17.5%; OR 0.84; 95% CI 0.39 to 1.79). Lewis et al. (1998)<sup>66</sup> found no difference between study groups in the six-month PPA (patch plus counselling — 9.7%; minimal care: 4.9%; OR 2.07; 95% CI 0.49 to 8.69). Nagle et al. (2005)<sup>136</sup> found no difference in the one-year PPA between intervention (6.8%) and control (7.7%) groups (OR 0.88; 95% CI 0.59 to 1.32). Mohiuddin et al. (2007)<sup>138</sup> showed that the CARs at six months, one year, and two years (55%, 39%, 33%) and PPA at six months and one year (60%, and 47%) were higher in the intervention group than those in the control group (13%, 11%, 9%, 15%, and 12% respectively). The respective ORs (95% CI) were 8.19 (4.09 to 16.41), 5.27 (2.53 to 10.99), 4.99 (2.26 to 11.02), 8.37 (4.29 to 16.34), and 6.69 (3.29 to 13.62). This trial was conducted among smokers who were admitted with a cardiovascular diagnosis. These patients have been shown to have higher rates of cessation than patients in other diagnostic groups. However, the relapse rates at one year compared to the quit rates at three months were higher in the intervention group (43%) than in the control group (27%). Molyneux et al. (2003)<sup>142</sup> and Simon et al. (1997)<sup>140</sup> made comparisons between study groups of one-year CAR (intervention 11%; control 7.6%; OR 1.50; 95% CI 0.54 to 4.13) and of one-year PPA rate (intervention 15%; control 8%; OR 2.15; 95% CI 1.01 to 4.56), respectively.

***NRT plus behavioural support versus behavioural support alone:*** Hand et al. (2002)<sup>155</sup> found that there were no differences in CARs at six months (16% versus 14%; OR 1.21; 95% CI 0.59 to 2.46) and one year (15% versus 14%; OR 1.08; 95% CI 0.52 to 2.23) between groups receiving NRT plus counselling and those receiving counselling. The relapse rates at one year were 46% in the NRT plus counselling group and 60% in the counselling group. Molyneux et al. (2003)<sup>142</sup> showed a difference between study groups (NRT plus counselling 11%; counselling 4.4%; OR 2.69; 95% CI 0.81 to 8.90), but the CI was wide. The relapse rates at one year between intervention and control groups were 33% and 50% respectively.

***Bupropion versus placebo:*** Both trials found no differences in the cessation rates between bupropion and placebo groups. Rigotti et al. (2006)<sup>170</sup> found the CARs and seven-day PPA rates at one year were 20% and 25% in the bupropion group compared with 14% and 21% in the placebo group. The ORs (95% CI) were 1.59 (0.81 to 3.12) and 1.26 (0.69 to 2.27), respectively. The relapse rates at one year compared with the quit rates at three months were 31% and 35% in the bupropion and placebo group, respectively. Simon et al. (2009)<sup>172</sup> found no difference in the validated six-month CAR between study groups (bupropion 15%; placebo 24%; OR 0.55; 95% CI 0.18 to 1.68).

## **Low-income smokers**

### ***Quality assessment***

Two trials used a pharmacotherapy intervention to help low-income smokers stop smoking. One trial<sup>128</sup> of nicotine patch versus nicotine patch plus behavioural support was rated A. One trial<sup>151</sup> of NRT plus behavioural support versus behavioural support was rated B.

### ***Summary of findings***

The results were summarized using a qualitative approach.

***Nicotine patch versus nicotine patch plus behavioural support:*** Solomon et al. (2000)<sup>128</sup> tested the impact of free nicotine patches plus proactive telephone peer support to help low-income women stop smoking. Of the 214 low-income women smokers, 108 were randomized to receive nicotine patch and 106 to receive nicotine patch plus proactive telephone support (provided by women ex-smokers who had received seven hours of training). A call was made weekly to bi-weekly for up to three months. There was no difference in PPA rates at six-month follow-up between the two treatment groups (19% nicotine patch versus 23% nicotine patch plus telephone, OR 0.78; 95% CI 0.40 to 1.51).

***NRT plus behavioural support versus behavioural support:*** Okuyemi et al. (2007)<sup>151</sup> assessed the efficacy of a motivational interview and nicotine gum for smoking cessation in low-income housing smokers. Sixty-six and 107 participants were randomized to receive nicotine gum plus counselling or counselling, respectively. The PPA rates at six-month follow-up were 7.6% and 9.3% in the nicotine gum plus counselling and counselling groups, respectively (OR 0.80; 95% CI 0.26 to 2.44).

## **Patients with cancer**

### ***Quality assessment***

One trial<sup>137</sup> of NRT plus behavioural support versus usual care in patients with cancer was rated B.

### ***Summary of Findings***

The results were summarized using a qualitative approach.

***NRT plus behavioural support versus usual care:*** Wakefield et al. (2004)<sup>137</sup> intended to determine whether a motivational interview plus nicotine patch compared with usual care could help patients with cancer quit smoking. Of 137 patients who were diagnosed with different types of cancer, 74 were randomized to be in the intervention group and 63 in the control group. The intervention group received a nicotine patch and behaviour intervention including specific advice

and booklets about the benefits of quitting, telephone counselling, and in-person counselling using the framework of a motivational interview. At the six-month follow-up visit, the seven-day PPA rates were not different between intervention (7%) and control groups (6%) (OR 1.07; 95% CI 0.27 to 4.16).

## 5 ECONOMIC ANALYSIS

### 5.1 Review of Economic Studies: Methods

A protocol that was developed for this report was followed throughout the analyses. An economic review was conducted for each article that met the selection criteria, to acquire information on costs, transition probabilities, and health utilities. Some of this information was used in our primary economic analyses. Another objective was to compare the results of existing studies with those obtained from our analyses.

#### 5.1.1 Literature searches

See section 4.1.1.

#### 5.1.2 Selection criteria

The authors of this report considered the following selection criteria to identify relevant economic studies:

**a) *Population, intervention, and comparators***

Selection criteria for population, intervention, and comparators were the same as in section 4.1.2. Economic studies that assessed the impact of copayment or payment on the cost-effectiveness of smoking cessation drugs were also selected.

**b) *Outcome***

Studies that reported incremental cost, incremental effectiveness (e.g., quality-adjusted life-years [or disability-adjusted life-year] gained, life-years saved [or death prevented], number of additional successful quitters), and/or incremental cost-effectiveness ratios (ICER).

**c) *Study design***

Studies that were cost-effectiveness analyses (CEA), cost-utility analyses (CUA), cost-minimization analyses (CMA), and/or cost-benefit analyses (CBA) were included. Studies based on CMA were selected only if justification of clinical equivalency was noted in the text.

#### 5.1.3 Selection method

Two reviewers (KA, KM) used the selection criteria to independently screen the titles and abstracts of all the citations that were retrieved during the literature search. Any disagreement was discussed and resolved. Once potentially included studies were selected, the full text of these selected articles was obtained. The reviewers independently reviewed the full text articles to select studies that met the selection criteria. Disagreements were resolved through discussion. Studies published in any language that met the inclusion criteria were selected. However,

translation was attempted only if the study results were considered to impact implications in this report. Articles were excluded if translation was unfeasible because of time or resource constraints. The review only included articles that published new data.

#### **5.1.4 Data extraction strategy**

One reviewer (KA) extracted information using the data extraction sheet (Appendix 9). Another reviewer (KM) ensured the accuracy of the data extraction. Disagreements were resolved through discussion.

#### **5.1.5 Strategy for validity assessment**

The Drummond et al. checklist was used to evaluate the level of rigour in the selected economic studies.<sup>4</sup> Poorly reported studies were interpreted with caution when obtaining parameter information and/or comparing our study results with those of these studies. It is important to note that most items in the checklist reflect the quality of reporting, which does not necessarily reflect model validity. For example, the appropriateness of the model structure and the selection of input parameters were not assessed by using the checklist.

#### **5.1.6 Data analysis methods**

The authors of this report considered a qualitative approach of summarizing studies. We focused on summarizing types of study population, interventions and comparators, study design, assumptions, main results, and input data.

### **5.2 Review of Economic Studies: Results**

#### **5.2.1 Study selection**

During a literature search conducted between October 2008 and February 2009, 1,642 citations were found. Fifty additional citations were found through periodic alerts obtained between April 2009 and July 2009. Two additional articles were found through handsearching. In total, 1,694 citations were found. The authors of this report did not identify any relevant economic studies through the grey literature search.

Of those 1,694 citations, 1,568 citations were excluded during screening based on the selection criteria. The remaining 126 potentially relevant articles were ordered in full text. We excluded 101 articles (Appendix 10), resulting in 25 economic studies to be included for a full-text review. The reasons for exclusions were:

- Study design (i.e., did not conduct CEA, CUA, CMA, or CBA): 19 articles
- Population (i.e., child cancer survivors,<sup>198</sup> military population,<sup>199</sup> and lung cancer patients<sup>200</sup>): three articles
- Intervention (i.e., did not consider pharmacological interventions): 41 articles
- Comparators (i.e., did not consider pharmacological interventions): 15 articles
- Outcomes (i.e., did not conduct incremental analyses): three articles
- Other reasons (e.g., non-English language, not an original study, a review article): 20 articles.

Appendix 11 summarizes the literature selection process.

## 5.2.2 Study characteristics

Appendix 12 summarizes information regarding the 25 included economic studies. Studies were conducted in various countries: Australia,<sup>201-203</sup> Japan,<sup>204</sup> The Netherlands,<sup>205-207</sup> the Seychelles,<sup>208</sup> Spain,<sup>209</sup> Sweden,<sup>210,211</sup> the UK,<sup>212-215</sup> and the US.<sup>216-224</sup> One study<sup>225</sup> conducted CEAs for Canada, France, Spain, Switzerland, the UK, and the US.

### a) *Population*

One study<sup>214</sup> assessed the cost-effectiveness of pharmacological interventions targeting heavy smokers (i.e., those who smoked more than 23 cigarettes per day). For other studies, some of which considered analyses by age and/or gender, the CEAs were targeting the general population.

### b) *Types of analysis*

Most studies considered CEAs<sup>201,203,205,207-209,212-214,216-218,222,225</sup> and/or CUAs<sup>202,204-207,210-212,215,219</sup> as study designs for economic evaluations. The outcomes for CUAs were quality-adjusted life-years (QALYs) gained (except for one study that used disability-adjusted life-years [LY] saved as an outcome<sup>202</sup>). The outcomes of CEAs were either cost per LY saved<sup>205,206,208,209,212-214,222,225</sup> and/or cost per additional quitter.<sup>201,203,205-207,212,216-218</sup> Four studies used CBAs.<sup>220,221,223,224</sup>

### c) *Model assumptions*

Many studies assumed the time horizon to be a lifetime.<sup>202,204-209,211,212,215,219,222,225</sup> Other studies considered a one-year time horizon;<sup>203,207,216,220,221,224</sup> most of these used efficacy data based on one RCT.<sup>207,216,220,221</sup> Two studies used a six-month time horizon,<sup>201,218</sup> and seven studies considered a time horizon longer than one year (but not lifetime).<sup>210,211,213,214,217,219,223</sup> Most studies assumed health care payer and/or societal perspectives. Five studies, most of which were CBAs, considered the employer perspective.<sup>217,220,221,223,224</sup> Most economic models assumed that an intervention occurred once at the beginning of the analysis period, but a few studies assumed life-time intervention (receiving one course of intervention yearly for a lifetime),<sup>222</sup> continued interventions for one, 10, and 75 years,<sup>205</sup> or NRT as a second-line intervention after a failure of bupropion therapy.<sup>202</sup>

### d) *Chronic conditions considered*

Various chronic conditions were considered in economic models, because smoking cessation interventions are expected to reduce the incidence of a number of smoking-related chronic conditions. Most frequently incorporated states were coronary heart disease (CHD) or myocardial infarction,<sup>204,205,205,206,209-211,213-215,215,217,219,223</sup> stroke,<sup>205,206,210,215,217,219,223</sup> COPD,<sup>204-206,210,211,213-215,217,219,223</sup> and lung cancer.<sup>204-206,209-211,213-215,219,223</sup> Asthma exacerbations were included in four studies.<sup>204,206,210,219</sup> Cancers of the larynx, oral cavity, and kidney were included in one study.<sup>205</sup> Igarashi et al.<sup>204</sup> included a number of other types of cancers (oropharyngeal, gastric, hepatic, rectal, cervical, and renal) and conditions such as aortic aneurysm dissection, apoplexy, and pneumonia. Cancers of the esophagus, pancreas, and bladder were included in both studies.<sup>204,205</sup> Two studies<sup>217,223</sup> incorporated pregnancy complications as a smoking-related morbidity health state.

### e) *Efficacy*

The efficacy of smoking cessation interventions was measured as abstinence rates in all economic studies, but the definition of abstinence rates varied. Most studies used CAR at six

months<sup>218</sup> or 12 months<sup>202,204,206,208,210-214,217,219,220</sup> as the efficacy measure. Two studies used seven-day PPA at six months<sup>207</sup> or 12 months<sup>216</sup> as the definition of treatment efficacy. One study also used PPA at 12 months with an unclear recall period.<sup>221</sup> The definition of abstinence was unclear in a number of studies.<sup>201,203,209,215,222-225</sup>

#### **f) Types of interventions**

Types of interventions considered in the selected cost-effectiveness studies can be summarized into five types of comparisons:

- comparisons across drug classes
- comparisons among NRTs
- comparisons of “bupropion plus NRT” therapy to other pharmacological therapies (i.e., cost-effectiveness of adding bupropion to NRT or vice versa)
- comparisons of “NRT plus behavioural” therapy to NRT therapy (i.e., cost-effectiveness of adding behavioural interventions)
- cost-effectiveness of paying or copaying for pharmacological interventions.

In most studies, these pharmacological therapies were provided with behavioural interventions (of various intensities) such as physician advice, counselling (e.g., by physicians, nurses, specialists, pharmacists, telephone, group, or individual), and/or motivational support.

### **5.2.3 Results from included studies**

The economic studies are summarized by the type of comparisons that were made.

#### **a) Cost-effectiveness across drug classes**

Ten studies assessed the cost-effectiveness of NRT and bupropion.<sup>202,203,205,210,212,215,217,221,222,225</sup>

In general, bupropion was found to be more effective and cost less than NRT. In other studies, bupropion was considered to be more cost-effective than NRT, or bupropion provided greater net benefit than nicotine patch.

Five studies conducted CEAs of bupropion and varenicline.<sup>211,217,219,220,222</sup> Compared with bupropion, three studies found that varenicline cost less and was more effective; and one study found that varenicline provided greater net benefit. The remaining two studies showed the incremental cost-effectiveness of varenicline (in reference to bupropion) to be US\$3,000 per LY gained<sup>222</sup> or €1,200 to €15,000 per QALY gained.<sup>211</sup>

Of three studies that compared NRT and varenicline, two found that varenicline was more effective and less expensive than NRT,<sup>206,219</sup> and if more expensive and effective, the ICER was between US\$20 to US\$130 per additional quitter.<sup>217</sup>

Two studies<sup>204,216</sup> modelled comparisons between bupropion or varenicline and placebo. In one study,<sup>216</sup> the cost-effectiveness of bupropion relative to placebo was US\$1,500 per additional quitter. Another study found that varenicline was more effective and less expensive than placebo for males, or the ICER (relative to placebo) was US\$1,500 to US\$5,200 per QALY gained for females.<sup>204</sup>

**b) Cost-effectiveness among NRTs**

Five studies assessed the cost-effectiveness of NRTs. In three studies,<sup>208,210,225</sup> nicotine patch was more cost-effective than spray, gum, and/or inhaler. Two studies concluded that gum was a more cost-effective strategy than patch,<sup>209,218</sup> spray, inhaler, and/or patch plus gum.<sup>218</sup> Such discrepancies in results could be due to differences in model settings among these studies; for example, country, study perspective, time horizon, and NRT dosage. Nonetheless, even if one strategy was more cost-effective than the other(s), the differences in incremental cost-effectiveness among the NRTs were comparable. For example, Gilbert et al.<sup>208</sup> compared all four NRTs and found that, in reference to counselling only, the incremental cost-effectiveness ratios were between US\$2,000 (patch) and US\$9,800 (spray) per LY saved.

**c) Cost-effectiveness of adding bupropion to NRT or vice versa**

The cost-effectiveness of adding bupropion to NRT was considered in five studies.<sup>201,202,212,218,221</sup> In one study, bupropion plus patch was found to be more effective and cost less than gum.<sup>218</sup> In other studies, adding bupropion to NRT provided greater net benefit than NRT alone,<sup>221</sup> or higher costs and effects (incremental cost-effectiveness of US\$8,000 per additional quitter). [The currency in the study was in 2003 Australian dollars: 1 Australian dollar is equivalent to US\$0.5633 (<http://www.bankofcanada.ca/en/rates/exchform.html>)].<sup>201</sup> In the assessment of cost-effectiveness of adding bupropion as a second-line therapy,<sup>202</sup> bupropion after nicotine patch resulted in an ICER of US\$5,200 per disability-adjusted LY averted in reference to the current practice that is defined by the study authors. [The currency in the study was in 2003 Australian dollars: 1 Australian dollar is equivalent to US\$0.5633 (<http://www.bankofcanada.ca/en/rates/exchform.html>)].

A cost-effectiveness analysis of adding NRT to bupropion found that adding the patch to bupropion plus counselling was more costly and less effective than bupropion plus counselling.<sup>201</sup> Similarly, another study found that adding the patch to bupropion generated lower net benefit than the use of bupropion without nicotine patch.<sup>221</sup> One UK study<sup>212</sup> assessed the cost-effectiveness of adding bupropion to NRT and adding NRT to bupropion. The study found that adding bupropion to NRT plus behavioural interventions resulted in ICERs of £1,600 to £3,300 per lifetime quitter, which was lower than the ICERs of adding NRT to bupropion plus behavioural interventions (£3,000 to £6,000 per lifetime quitter). The results were consistent when outcomes were expressed as cost per LY or cost per QALY gained.

**d) Cost-effectiveness of adding behavioural interventions**

One study considered the cost-effectiveness of adding specialist smoking cessation services (a clinical nurse specialist) to brief advice plus self-help materials plus NRT.<sup>213</sup> The study found that, depending on the perspective that was chosen (UK health authority or societal), adding specialist smoking cessation services could be more cost-effective or less cost-effective than an intervention without the specialist smoking cessation services in reference to the current practice as defined by the study author. In any case, the ICER (in reference to current practice) for interventions with or without the specialist smoking cessation services was between £255 and £873 per LY gained. Another study<sup>224</sup> found that adding a five-day behavioural program, pharmacists' consultations, or both to the nicotine patch therapy provided greater net benefit than nicotine patch monotherapy. However, this study also concluded that adding five weekly individual counselling visits to nicotine patch did not add any benefit to the use of nicotine patch.

**e) Cost-effectiveness of paying or copaying for pharmacological interventions**

Three studies that assessed paying or copaying for pharmacological interventions concluded that reimbursing for NRT or bupropion was a cost-saving or cost-effective option for society, private payers, or public payers.<sup>207,214,223</sup> From the societal perspective, Kaper et al.<sup>207</sup> found that reimbursing for NRT, bupropion, and behavioural counselling was cost-effective, assuming (by the study authors) that Dutch society was willing to pay €18,000 per QALY gained. Akehurst and Piercy<sup>214</sup> also showed that if NRT was not reimbursed, the cost to the UK National Health Services for treating smoking-related diseases could exceed savings from not reimbursing NRT. Halpern et al.<sup>223</sup> found that, for every dollar spent on covering bupropion prescriptions, a managed care plan could save between US\$4 to US\$7 by saving costs incurred because of smoking-related acute and chronic conditions, absenteeism, and decreased productivity.

After our first literature search was completed in February 2009, the authors of this report identified (between March 2009 and March 2010) six additional cost-effectiveness studies targeting a general population of smokers<sup>226-231</sup> that met the economic study inclusion criteria. In general, the results from these studies were comparable to those of the studies that have been summarized above, with respect to overall conclusions about the relative cost-effectiveness among NRT, bupropion, and varenicline. Five of the six studies<sup>226-228,230,231</sup> were funded by the manufacturer of varenicline and were based on a decision-analytic model that was used in other studies of varenicline funded by the same manufacturer.<sup>204,206,211,217,219</sup> Bae et al.<sup>228</sup> (Korea) and Annemans et al.<sup>226</sup> (Belgium) assessed the cost-effectiveness of varenicline, bupropion, and NRT. Bae et al. found that bupropion was more expensive and generated less benefit than varenicline and NRT. Moreover, the cost-effectiveness of varenicline compared with NRT was between US\$3,900 and \$16,500 per QALY gained, depending on the population (male, female, or both) and model assumptions. Annemans et al.<sup>226</sup> found that, compared with bupropion and NRT, varenicline was less expensive and generated more benefit. Bolin et al.<sup>227</sup> assessed the cost-effectiveness of varenicline compared with NRT in Belgium, France, Sweden, and the UK. Except in France, varenicline was found to cost less and generated more benefit compared with NRT, with respect to cost per QALY gained. In France, the ICER of varenicline versus NRT was €2,803 per QALY gained. A study by van Schayck et al.<sup>229</sup> conducted the cost-effectiveness analysis of bupropion (plus counselling) versus placebo (plus counselling) therapies along with a 12-week RCT. The results showed that the ICER of the bupropion arm compared with the placebo arm was €2,097 per additional quitter. Linden et al.<sup>231</sup> compared the cost-effectiveness of unaided cessation, bupropion, and varenicline in the general Finnish population. The study found that varenicline was less expensive and generated more benefit over bupropion and unaided cessation. Knight et al.<sup>230</sup> assessed the cost-effectiveness of 24-week varenicline therapy (12-week initial therapy plus 12-week maintenance therapy) compared with 12-week varenicline treatment, bupropion, and NRT in a general US population. The results showed that both 24-week and 12-week varenicline therapies were less expensive and generated more benefit than bupropion and NRT. The ICER of the 24-week varenicline therapy compared with the 12-week therapy was US\$972 per QALY gained.

A review of existing studies showed that, in general, varenicline dominated (i.e., cost less and was more effective) or was more cost-effective than NRT and bupropion. Studies also showed that bupropion dominated or was more cost-effective than NRT. However, the review highlighted a lack of economic evaluation studies of pharmacological interventions. This was evident in particular regarding:

- economic evaluation of varenicline with other pharmacological interventions, particularly non-industry sponsored studies
- assessment of adding behavioural interventions to pharmacological therapies
- paying or copaying for pharmacological therapies.

Moreover, none of the selected studies was based solely on a Canadian setting. These findings lead the authors of this report to conduct a CEA and a CUA of pharmacological interventions from a Canadian perspective. Many of the CEAs and CUAs were conducted using a Markov-model approach, accounting for smoking-related chronic conditions. Markov model-based CUAs are particularly useful because they allow the inclusion of short-term (i.e., quit rates) and long-term (i.e., LYs and QALYs) impacts of smoking cessation interventions. An inclusion of quality of life information in the economic modelling is important, considering that the smoking-related chronic conditions are often long-lasting, and they impact not only life expectancy but also the health-related quality of life of smokers.

#### 5.2.4 Quality assessment

Overall, the reporting of selected studies was comprehensive, based on the Drummond et al. quality checklist (Appendix 13). Most studies appropriately described study objectives, comparators, viewpoints, identification of costs and outcomes and their measurements, and study results. However, a number of studies did not provide a clear description of and a rationale for the efficacy data (i.e., quit rates) that were used. For example, several studies provided a few sources for efficacy data without clear descriptions of how the evidence was summarized.<sup>203,208,209,215,223,224</sup> In a few studies, the methods for cost valuations were also not clearly reported and/or justified.<sup>206,207,211,219,220,225</sup> Issues of generalizability, distribution, and implementation were not clearly stated in a number of articles.<sup>204,205,207,211,212,214,215,219,220,222,223,225</sup> Parameter uncertainties were assessed in most studies (deterministically and/or probabilistically). However, six studies<sup>203,209,213,217,220,223</sup> did not report the assessment of uncertainty or if assessed, the results were not clearly reported. Almost half of the studies did not provide comprehensive discussions of generalizability, distributional, and implementation issues. In particular, study implications that were related to the latter two aspects were lacking.

### 5.3 Primary Economic Evaluation: Methods

The primary objective of the economic evaluation was to assess the relative cost effectiveness of alternative smoking cessation interventions. Analysis was facilitated by the construction of a model which estimated the number of smokers who successfully quit through each intervention and the benefits of smoking cessation on mortality and morbidity.

#### 5.3.1 Types of economic evaluation

The choice of an appropriate study design depends on whether alternative interventions result in differences in the number of quitters, mortality, and/or morbidity. In the case of smoking cessation interventions, the authors of this report expected important differences in such outcomes.<sup>206,212</sup> Primary analysis was in the form of a cost-utility analysis (cost per QALY gained). Secondary analyses were in the form of cost-effectiveness analyses (cost per additional quitter and cost per LY saved).

### 5.3.2 Target population

The target population was consistent with that described in the clinical section (i.e., general and specific populations who were motivated to quit smoking). Economic modelling was considered for populations where evidence of clinical efficacy was reported.

The base analysis focused on a 20 year old male smoker given that this is the cohort with the highest number of attempted quitters in Canada (Appendix 24). Analyses for other age-gender cohorts are reported in detail in Appendix 20. For other analyses (i.e., relating to specific populations, adding behavioural intervention and payment or copayment of the smoking cessation interventions), the age of the population reflected study populations from which the clinical efficacy results were derived.

### 5.3.3 Comparators

Consistent with the clinical analyses, the comparators were NRT (patch, gum, inhaler and lozenge), bupropion, varenicline, and no intervention (or placebo). In the clinical analyses, there was evidence of efficacy for NRT spray and sublingual. However, they were not considered in the economic analyses because they are not currently approved in Canada.

For the cost-effectiveness of adding behavioural interventions, we considered comparisons of pharmacological alone versus pharmacological plus behavioural interventions. To assess the cost-effectiveness of paying or copaying for pharmacological interventions, studies (reported in the clinical section of this report) that described the efficacy of pharmacological interventions with or without insurance coverage were considered.

### 5.3.4 Perspective

The model adopted a perspective of the publicly funded health care system. This is consistent with the CADTH's Guidelines for the Economic Evaluation of Health Technologies.<sup>232</sup>

### 5.3.5 Effectiveness

Tables 1 to 4 show the efficacy data (i.e., quit rates) that were used in our main analyses for each economic research question.

For assessing cost effectiveness in both general and specific populations, the authors of this report considered the following criteria to select clinical efficacy data that were used for the construction of the economic models:

- Efficacy data comparing at least two interventions
- Efficacy data presented as 12-month CAR
  - We considered 12-month CAR as the baseline definition of efficacy because this definition of abstinence was most often used in existing economic analyses. It is also the most conservative measure of quitting smoking. We acknowledge that other definitions of quit rates such as six-month CAR, 12-month PPA, or continuous abstinence are also important in clinical practice. Therefore, where clinical evidence was available, we considered other definitions of quit rates in sensitivity analyses.

- Clinical efficacy results in our economic analyses only if the study population was transparent.
  - For example, when assessing cost-effectiveness for specific populations, we did not consider efficacy results if the baseline patient characteristics such as distribution of co-morbidities in the trials were unclear, preventing us from identifying the initial cohort size in each disease state.

To assess the cost-effectiveness of adding behavioural interventions, the authors also selected the meta-analysis results with 12-month continuous abstinence as the primary outcome.

To assess the cost-effectiveness of paying or copaying for pharmacological interventions, three clinical trials that met the clinical inclusion criteria were not pooled because of heterogeneity concerns. Therefore, the economic study was conducted using results from one study<sup>195</sup> that assessed the effect of reimbursing NRT and bupropion, which was considered to be most applicable to our research question.

**a) Clinical efficacy of general population**

The quit rates for the general population were taken from our Bayesian MTC meta-analyses of drug versus placebo trials that included healthy and motivated-to-quit populations (Table 1). Because not all smokers who attempt to quit smoking rely on smoking cessation interventions, an electronic search of published articles was conducted to identify a spontaneous quit rate (i.e., a quit rate without smoking cessation intervention). For the base-case analysis, we considered the spontaneous quit rate as the quit rate for the “no intervention” option. Based on 11 studies reviewed, the spontaneous quit rates varied from 1%<sup>212,214,233</sup> to 27%,<sup>234</sup> with varying definitions of quit rates. The base-case spontaneous cessation rates appear in Table 1. The 12-month abstinence rates were based on a US prospective study of 414 community residents.<sup>234,235</sup> Biochemically verified six-month abstinence rates were unavailable from this study. Therefore, the six-month abstinence rates were based on a US study of 71 hospital employees.<sup>234</sup> These rates were based on the biochemically verified rate, which are consistent with our clinical inclusion criteria.

We also conducted sensitivity analyses using the placebo quit rate as the quit rate of the “no intervention” option. This was because the spontaneous quit rate may be partly derived from those who were not motivated to quit, which may have underestimated spontaneous cessation rates; although, it is in general the case that placebo groups receive standard behavioural interventions. We considered that both placebo and intervention groups receive a common behavioural intervention so that the incremental analyses were consistent with the case, with or without taking account of the common behavioural intervention.

The effectiveness of cessation interventions was measured by the odds ratio (OR) compared to placebo. The ORs and estimated quit rates are presented in Table 1. The quit rate for the interventions ( $p_i$ ) were estimated by the following formula:  $p_i = \frac{e^{\ln OR}}{(1 - p_0) + (p_0) * (e^{\ln OR})} \cdot p_0$ , where  $p_0$  is a quit rate for “no intervention” (i.e., spontaneous quit rate or placebo quit rate).<sup>206</sup>

Uncertainties around the natural log of OR ( $\ln[OR]$ ) were considered in probabilistic analyses based on a normal distribution.<sup>236</sup> Uncertainties around spontaneous quit rates were assessed assuming a beta distribution, with alpha being the number of quitters, and beta = [total study sample size] – [number of quitters], which were obtained from Cohen et al.<sup>234</sup>

<b>Table 1: Clinical Efficacy of Smoking Cessation Interventions Used for Base-Case Analyses of General Population (CAR at 12 months)</b>			
<b>Intervention</b>	<b>OR versus no intervention</b>	<b>Log OR (SE)</b>	<b>Quit Rate</b>
No intervention			0.034 <sup>*234,235</sup>
NRT Patch	1.77	0.573 (0.102)	0.059
NRT Gum	1.68	0.518 (0.146)	0.056
NRT Inhaler	2.24	0.807 (0.240)	0.073
NRT Lozenge	2.31	0.838 (0.253)	0.075
Bupropion	1.93	0.657 (0.120)	0.064
Varenicline	2.73	1.004 (0.126)	0.088

CAR = continuous abstinence rate; NRT = nicotine replacement therapy; OR = odds ratio; SE = standard error.  
<sup>\*</sup> Beta distribution based on alpha = 14, beta = (414-14) = 400.<sup>234</sup>

**b) Clinical efficacy of adding behavioural intervention to pharmacological intervention**

Evidence on the clinical efficacy of adding a behavioural intervention was reported in our Bayesian MTC meta-analysis results, which were based on Lando et al.<sup>125</sup> In Lando et al., 12-month and six-month CARs of NRT patch versus NRT patch plus telephone counselling plus smoking helpline were reported (Table 2). The quit rates for NRT patch (reference case) were based on the number of study participants and quitters reported in the study. Based on Lando et al.,<sup>125</sup> of 347 subjects who were in the NRT patch group, 52 and 46 and were confirmed to be continuously abstinent at six and 12 months, respectively (i.e., CAR at six months was 0.150 [= 52/347] and CAR at 12 months was 0.133 [= 46/347]).

The effectiveness of adding a behavioural intervention was measured by the odds ratio (OR) compared to no behavioural intervention. The ORs and estimated quit rates are presented in Table 2. The quit rate for adding a behavioural intervention was derived as for the base analysis

Uncertainty around  $\ln(OR)$  was defined in the same way as for the analysis for the general population. Uncertainty around baseline quit rates (i.e., NRT patch group) was defined as beta distributions with alpha = 46 and beta = 301 for CAR at 12 months and with alpha = 52 and beta = 295 for CAR at six months.

<b>Table 2: Clinical Efficacy of Smoking Cessation Interventions Used for Base-Case Analyses of Adding Behavioural Interventions to NRT Patch (CAR at 12 months)</b>			
<b>Intervention</b>	<b>OR versus NRT Patch</b>	<b>Log OR (SE)</b>	<b>Quit Rate</b>
NRT Patch			0.133
NRT Patch + Behaviour	0.96	-0.039 (0.287)	0.128

CAR = continuous abstinence rate; NRT = nicotine replacement therapy; OR = odds ratio; SE = standard error.

**c) Clinical efficacy of paying or copaying for pharmacological intervention**

Results shown in Kaper et al.<sup>195</sup> were used to obtain quit rates and relative risks of reimbursing or not reimbursing for smoking cessation interventions including NRT (gum, patch, sublingual, and inhaler), bupropion, and various types of behavioural counselling. In addition, changes in the effective price of smoking cessation intervention to patients are expected to impact the use of smoking cessation products. Therefore, the probability and relative risk of using smoking cessation interventions for cases with and without reimbursement were incorporated in the analyses.

The study by Kaper et al. was a randomized trial that assigned a random sample of general adult smokers to intervention (full reimbursement) or control (no reimbursement) groups and compared quit rates and use of smoking cessation interventions between the two groups. The sample size of the intervention group was 634, and the sample size of the control group was 632. At the end of six months, 68 in the intervention group and 26 in the control group reported having used smoking cessation interventions. Of those who used smoking cessation interventions, 35 of those who received full reimbursement (i.e., 35/68 = 51.5%) successfully quit smoking, and 18 of those who did not receive any reimbursement (i.e., 18/26 = 69%) successfully quit smoking. Therefore, the probability of smoking cessation intervention usage was higher and the subsequent quit rates were lower among those with full coverage compared with those without any coverage. Using this information, Table 3 shows the parameters that were used in the economic modelling.

Parameter uncertainties were assessed with respect to the probability of using smoking cessation interventions and quit rates for the “no reimbursement” group using beta distributions (alpha = 26 and beta = 608 for the probability of smoking cessation intervention use; alpha = 18 and beta = 8 for the quit rate). The uncertainties around the relative risks of the smoking cessation intervention use and quit rates of the “full reimbursement” group were assessed using the normal distribution around ln (RR).

<b>Table 3: Efficacy of Reimbursing for Smoking Cessation Interventions Used for Base-Case Analyses</b>			
<b>Intervention</b>	<b>Quit Rates</b>	<b>RR<sup>*</sup></b>	<b>lnRR (SE)<sup>*</sup></b>
<b>Use of smoking cessation interventions</b>			
No reimbursement	0.041	1	---
Full reimbursement	0.108 <sup>†</sup>	2.624	0.965 (0.224)
<b>Quit rates (point prevalence abstinence at 6 months)</b>			
No reimbursement	0.069	1	---
Full reimbursement	0.515 <sup>‡</sup>	0.743	-0.296 (0.176)

RR = relative risk; SE = standard error.

\*Relative risk (RR) and standard errors of ln(RR) [lnRR(SE)] calculated using standard formula.<sup>237</sup>

†Calculated by multiplying probability of smoking cessation intervention use for no reimbursement by relative risk of smoking cessation intervention use

‡ Calculated by multiplying quit rate of no reimbursement group by relative risk of cessation.

**d) Clinical efficacy of specific populations**

The meta-analysis results for two specific populations (cardiovascular or smoking-related diseases, and hospitalized patients) were considered in our analysis, because they provided comparisons of more than two pharmacological interventions and 12-month CAR (Table 4). Our

Bayesian meta-analyses targeting cardiovascular or smoking-related diseases were based on three trials.<sup>96,121,179</sup> Tonstad et al.<sup>179</sup> compared bupropion versus placebo; Hjalmarsen<sup>96</sup> compared NRT gum versus placebo; and Tønnesen and Mikkelsen<sup>121</sup> compared four interventions (NRT patch, NRT inhaler, NRT patch plus inhaler, and placebo). We did not consider the spontaneous quit rate as the reference quit rate in the analysis for specific populations because the spontaneous quit rates that were used in our analyses do not necessarily represent those for specific populations. Therefore, we only considered the placebo quit rates that were reported in our Bayesian meta-analyses as the quit rate for the no intervention group.

The effectiveness of cessation interventions was measured by the OR compared to placebo. The ORs and estimated quit rates are presented in Table 4. The quit rate for an intervention was derived as for the base analysis.

Consistent with other analyses, uncertainties around quit rates for no intervention groups were based on the beta distribution with means (quit rates) and standard errors reported in Table 4. Uncertainties around the efficacy of NRT and bupropion were assessed assuming normal distributions around  $\ln(\text{OR})$ .

<b>Table 4: Clinical Efficacy of Smoking Cessation Interventions Used for Base-Case Analyses of Specific Populations (CAR at 12 months)</b>			
<b>Interventions</b>	<b>OR</b>	<b>Log OR (SE)</b>	<b>Quit Rate</b>
<b>Patients with cardiovascular or smoking-related diseases</b>			
NRT**	2.66	0.977 (0.734)	0.204
Bupropion	2.82	1.035 (0.980)	0.214
<b>Hospitalized patients</b>			
No intervention			0.149 (SE = 0.078)
NRT patch	1.60	0.471 (1.160)	0.219
Bupropion	1.56	0.445 (1.217)	0.215

CAR = continuous abstinence rate; NRT = nicotine replacement therapy; OR = odds ratio; SE = standard error.

\*\*Gum, patch and/or inhaler.

### 5.3.6 Time horizon

For the primary analysis, a lifetime time horizon (up to the age of 100 years) was assumed because the morbidity that is associated with smoking is often chronic. Therefore, it is likely that meaningful differences in costs and outcomes among alternative interventions may not become apparent in a model with a shorter time horizon. The secondary analysis using life years as the outcome measure also adopted a lifetime horizon. The secondary analysis using quitters as an outcome used a one year time horizon.

### 5.3.7 Modelling

The effects of smoking cessation interventions on costs and outcomes were assessed using a Markov cohort simulation model that were based on previous economic models.<sup>206,211,219,238</sup> A Markov model was appropriate to address our research questions because most states in our

analysis, such as long-term cessation and chronic conditions, were recursive. The Markov cohort simulation and value of information analyses were conducted in Microsoft Office Excel 2003.

The Markov model employed in the base analysis for assessing the general population was the basis of all other analyses. Male and female populations were modelled separately because even though efficacy data were not reported by gender, it was reasonable to consider gender-specific smoking-related disease risks.

The Markov model consisted of three components:

- Modelling of smoking status during the first 12 months since the initiation of the cessation intervention (Figure 7)
- Modelling long-term transitions across four smoking states (Figure 8)
- Modelling transitions across major smoking-related chronic conditions (Figure 9).

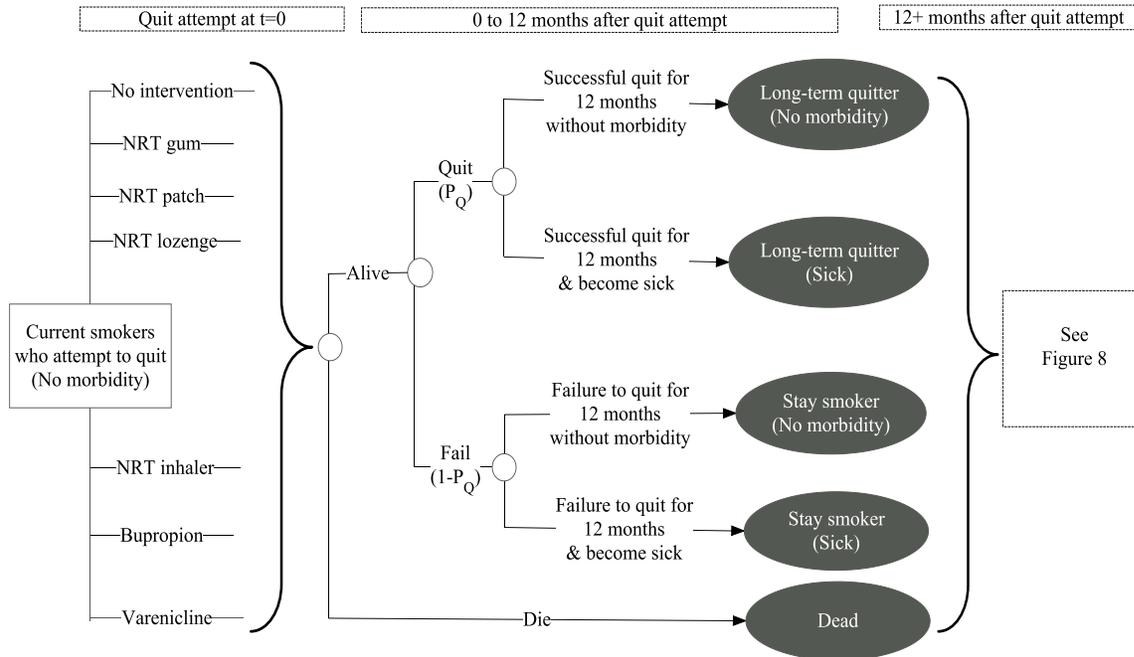
Thus modelling of the chronic conditions is conditional on smoking status. The authors of this report defined a long-term quitter as someone who continues to be abstinent after 12 months, given that the quit attempt is often short-lasting.<sup>238</sup> We compared these models by reflecting the costs and clinical efficacy of each treatment option. Then, the total costs and outcomes of the various treatment options were compared in cost-effectiveness and cost-utility analyses.

### **Smoking status (0 to 12 months)**

In the first cycle, a cohort of smokers without any smoking-related morbidity who attempt to quit smoking receives one of the smoking cessation interventions (Figure 7). At the beginning of the model, a cohort of smokers receives a one-time cessation intervention (or no intervention for those in the reference group). After the cessation intervention, the cohort is divided between the following states:

- Successful quit for 12 months without smoking-related morbidity (“Long-term quitter [No morbidity]”)
- Successful quit for 12 months and become sick (“Long-term quitter [Sick]”)
- Failure to quit for 12 months without morbidity (“Stay smoker [No morbidity]”)
- Failure to quit for 12 months and become sick (“Stay smoker [Sick]”)
- Die from any cause (“Dead”).

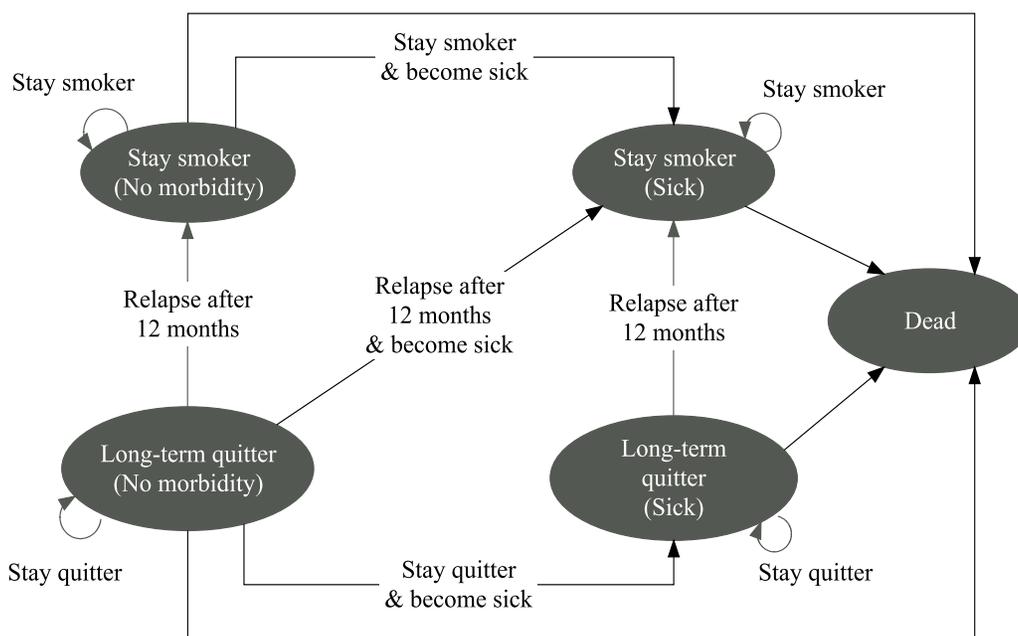
**Figure 7: Smoking Status Model (0 to 12 Months)**



### Smoking status (more than 12 months after intervention)

In subsequent cycles for the remaining time horizon, smoking status is continued to be modelled (Figure 8). When a cohort reaches “Long-term quitter (No morbidity),” they will stay abstinent with or without developing a chronic condition (“Long-term quitter [Sick]” or “Long-term quitter [No morbidity]”), relapse with or without developing a chronic condition (“Stay smoker [Sick]” or “Stay smoker [no morbidity]”), or die from any cause (“Dead”). Those in the “Long-term quitter (Sick)” state will stay abstinent with morbidity, relapse with morbidity (“Stay smoker [Sick]”), or die from smoking-related morbidity or any other causes (“Dead”). Those in the “Stay smoker (Sick)” state will continue to smoke or die from smoking-related morbidity or any other causes.

**Figure 8: Smoking Status Model (12 Months After Intervention)**



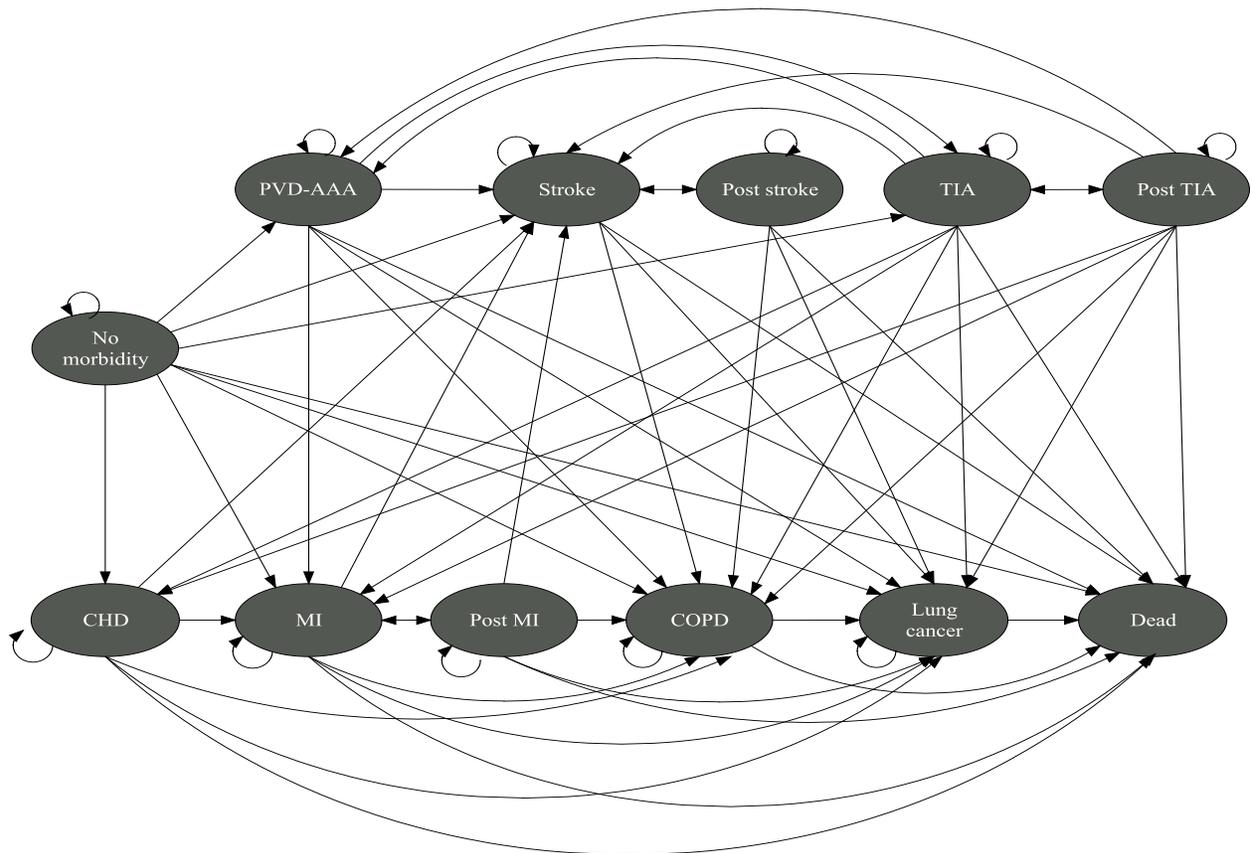
### Chronic condition modelling

Above, the modelling of chronic conditions is simplified in description as simply being “Sick”. In reality the model is much more complex. In any of the smoking-related states described previously, cohorts of smokers or quitters face risks of eight major smoking-related chronic conditions: transient ischemic attack (TIA); stroke, exacerbations of asthma; chronic obstructive pulmonary disease (COPD); lung cancer; coronary heart disease (CHD); myocardial infarction (MI); or peripheral vascular disease or abdominal aortic aneurysm (PVD-AAA) (Figure 9). The authors of this report considered these as major smoking-related morbidities because, together, these conditions accounted for at least 75% to 85% of smoking-attributable deaths.<sup>239,240</sup> In this way, we made the decision model parsimonious without compromising its representativeness. Nonetheless, smoking certainly impacts other conditions. For example, bladder, pancreatic, liver, colorectal, oral, and esophageal cancers are also important, and renal disease, osteoporosis, type 2 diabetes, cataracts, and macular degeneration are all related to smoking. However, lung cancer was the major type of cancer, accounting for more than 75% of smoking-attributable deaths among 11 types of cancer.<sup>239</sup> Therefore, in decision analytic models targeting general populations, we considered these health states to be sufficient to describe the progress of smoking-related chronic conditions. It has been considered that smoking has preventive effects on Alzheimer disease or Parkinson disease. However, we did not account for such putative benefits because the evidence of such effects is limited.

In addition to excluding less frequent conditions, the model is further parsimonious in that it does not model combinations of chronic conditions - rather the model only allow transitions from one health state to a more detrimental condition. For example, the model allows the transition from the TIA states to lung cancer as lung cancer is both more costly to treat and has a greater impact on morbidity and mortality. However, the model does not consider the transition from lung cancer to TIA. The authors of this report assumed that an asthma exacerbation was an acute and

non-fatal event that lasted one week. Therefore, the asthma exacerbation state was not included in Figure 9. Instead, the costs and utilities that were associated with an asthma exacerbation were incorporated separately in each cycle to calculate total costs and QALYs.

**Figure 9: Chronic Condition Model**



CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PVD-AAA = peripheral vascular disease or abdominal aortic aneurysm; TIA = transient ischemic attack.

The following major assumptions were made in the economic model:

- A cohort of smokers receives a one-time intervention at the beginning of the smoking status model (0 to 12 months); i.e., no re-intervention or switching to an alternative treatment when the initial intervention fails.
- The initial cohort consists of a group of current smokers who are motivated to quit smoking without any specified smoking-related morbidity.
- Long-term quitters are defined as those who continue to be abstinent for 12 months.
- The long-term relapse rates depend only on time since cessation.
- The adverse events associated with interventions are not considered.
- The incidence of smoking-related morbidities is assumed to be zero for those under the age of 30 years (unless there were incidence data on those under the age of 30 years).
- Combination of conditions is not modelled, except asthma exacerbation can occur simultaneously with another chronic condition.

## Transition probabilities

### *Transition probabilities of smoking status models*

The quit rates and long-term relapse rates were transition probabilities that were required in smoking status models (Figures 7 and 8). Quit rates were presented in the earlier section. The long-term relapse rates were the relapse rates after a smoker has become a long-term quitter. They were obtained from electronic and handsearches of published articles. We selected the long-term relapse rates that were reported by Wetter et al.,<sup>241</sup> which was a community-based, four-year longitudinal study of former smokers. Wetter et al. was considered appropriate because it was a community-based study and allowed the calculation of relapse rates up to nine years after cessation using baseline and follow-up information. Moreover, results in Wetter et al. were comparable with those in a number of other reviewed studies. Although we found one Canadian study,<sup>242</sup> it only reported two-year relapse rates.

Based on Wetter et al.,<sup>241</sup> the annual probabilities of relapse in years two to five, six to seven, eight to 10, and 11+ since quitting were 0.087, 0.038, 0.021, and 0.005 respectively (Table 5). The uncertainties were assessed around four-year relapse rates using a beta distribution. Then, the four-year relapse rates were converted to annual probabilities using the following non-linear transformation:  $P = 1 - \exp(\ln(1 - p_t)/t)$ , where  $p_t$  is a  $t$ -year relapse rate (here,  $t = 4$ ).<sup>236</sup> A beta distribution was assumed for the four-year relapse rate,  $p_t$ .

Years Since Quitting	Annual Probability	Distribution**
2 to 5	0.087	Beta (alpha = 24, beta = 55 [=79-24])
6 to 7	0.038	Beta (alpha = 11, beta = 68 [=79-11])
8 to 10	0.021	Beta (alpha = 15, beta = 172 [=187-15])
11+	0.005	Beta (alpha = 15, beta = 703 [=718-15])

\*Source: Wetter et al.<sup>241</sup>

\*\*Long-term relapse rate at two to five years was obtained based on finding from Wetter et al. that, of 79 respondents who reported to have been abstinent for four to 12 months at baseline, 24 (30.6%) reported relapse during the four-year follow-up period. Similarly, for relapse rate at six to seven years, it was reported that, at baseline, 79 respondents were abstinent for one to two years and, among the 79 respondents, 11 (14.5%) relapsed during follow-up. For relapse rate at eight to 10 years, 187 respondents reported to have been abstinent for two to five years at baseline and, of those, 15 (8.2%) relapsed during follow-up. For 718 respondents who were reported to have been abstinent for more than five years at baseline, 15 (2.1%) relapsed during follow-up.

### *Transition probabilities of chronic condition models*

The authors of this report reviewed published cost-effectiveness studies that were retrieved from the Cost Effective Analyses Registry Database<sup>243</sup> and articles found by handsearching to identify the transition probabilities that were used in the chronic condition model (Figure 9). We also searched for information presented in articles that were included in our economic review. The incidence rates of chronic conditions were used for the transition probabilities from the “no morbidity” state and were based on electronic and handsearches of published articles and grey literature. The incidence rates were calibrated further so that they reflect the rates for smokers and quitters. Then, the incidence of each chronic condition was converted to probabilities using non-linear transformation.<sup>236</sup> Appendix 14 (Section I) describes the steps of calibration.

We preferred information that was based on the Canadian general population and/or health states that closely reflected those used in our model. For consistency, efforts were made to select articles that covered as much information as possible in one study. For example, the transition

probabilities that were associated with vascular disease states (MI, PVD, stroke) were available from Karnon et al.,<sup>244</sup> and were estimated based on UK-based registries and a six-year cohort study of 607 patients. We did not identify any Canadian studies that were as comprehensive as Karnon et al. The transition probabilities of chronic condition states are described in Appendix 14 (Section II). The transition probabilities that were not reported as annual probabilities in original articles were transformed to annual probabilities using a non-linear transformation presented earlier.<sup>236</sup>

The all-cause mortality was based on data from Canadian life tables.<sup>245</sup> All-cause mortality of quitters and smokers was estimated such that the all-cause mortality of quitters was lower than that of smokers.<sup>215</sup> Appendix 15 describes the steps that were used to obtain age- and gender-specific all-cause mortality by smoking status. In the model validation step (subsequently described), our model was found to underpredict the survival of smokers and quitters. This was particularly the case for smokers over 30 years old, when cohorts started to develop a series of smoking-related chronic conditions. To adjust for the underprediction, the authors of this report calibrated all-cause mortality and assumed further that the all-cause mortality rates of smokers and quitters were the same as those of non-smokers after the age of 30 years. This means that we assumed no excess mortality for smokers and quitters compared with non-smokers after accounting for the mortality resulting from smoking-related morbidity considered in our model.

### **Relative risk of developing chronic conditions by smoking status**

The differential risks of developing smoking-related diseases between current smokers and quitters were obtained from an electronic search of published articles and from the included economic studies. A complete list of relative risks and detailed descriptions are in Appendix 14 (Table A12). The relative risks of COPD, lung cancer, CHD, and stroke were obtained from a six-year follow-up study targeting more than 970,000 in the US general population.<sup>219,246</sup> Following Howard et al.,<sup>219</sup> the relative risks of asthma emergency visits were used as a proxy for the relative risks of asthma exacerbations. The authors of this report also found data based on the US national asthma surveillance. However, the data were not reported by smoking status.<sup>247</sup> The relative risk of PVD-AAA was based on a five-year study of 1,592 adults in Scotland.<sup>248</sup> Using the baseline smoking status information (smoker or recent quitter [quit less than five years ago], or never smoker or long-time quitter) and the health status at five years (developed PVD or stayed healthy), we calculated the relative risks of developing PVD by smoking status (see Appendix 14, Table A13 for details). Because there was no distinction between smokers and quitters, we assumed the same relative risk for smokers and quitters. We also found a study by Auerbach and Garfinkel<sup>249</sup> that provided relative risk of AAA by smoking status. However, we did not consider this study because it was dated and the derivation of the relative risk was unclear. The relative risk of developing TIA by smoking status was based on a study of 25,538 participants in Germany.<sup>250</sup> The relative risk of TIA by smoking status was reported based on Cox proportional hazard models adjusting for gender, education, and other potential risk factors of TIA. The standard error of the natural log of the hazard rate ( $\ln[HR]$ ) was calculated using the standard formula based on the CI that was reported in the study.<sup>251</sup> The relative risk of MI was based on a Dutch study.<sup>205</sup> The standard error of the relative risk of MI was not reported, and was assumed to be 10% of its point estimate.

The authors of this report used these relative risks to calculate the transition probabilities from “no morbidity” to each chronic health state. This implies that the probability of developing a first chronic condition depends on age, gender, and smoking status. However, once a cohort develops a chronic condition, the risk of developing an additional condition only depends on the current health state, age, and gender, and therefore is independent of smoking status. Uncertainties around relative risks were assessed by assigning the normal distribution to  $\ln(HR)$ .

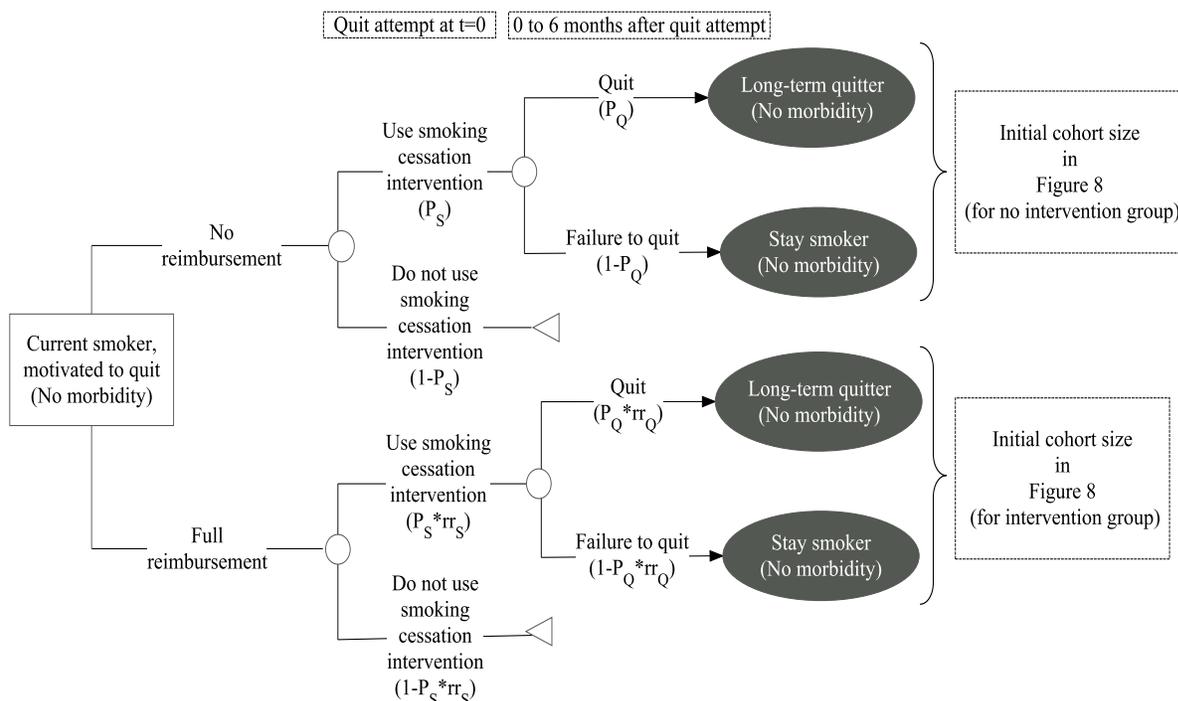
**Modelling the cost-effectiveness of adding behavioural program to pharmacological interventions**

The model structure that was used to assess the cost-effectiveness for the general population was applied to assess the cost-effectiveness of adding a behavioural program. The age at intervention was set at 40 years, which corresponds approximately to the baseline mean age that was reported in the study on which the clinical efficacy was based.<sup>125</sup>

**Modelling the cost-effectiveness of paying or copaying for pharmacological interventions**

The model structure for assessing the cost-effectiveness of paying or copaying for pharmacological intervention differed slightly from those used to answer other research questions. This was because, in addition to quit rates, we considered the differential probabilities of using smoking cessation intervention use between those with or without reimbursement. Therefore, the role of the smoking status model (0 to 12 months) in Figure 7 was modified such that the model determined the initial population of smokers with or without reimbursement, which was used as the initial cohort size of the smoking status model in Figure 8. The one study (Kaper et al.<sup>195</sup>) that provided sufficient parameter information reported a six-month quit rate instead of a quit rate at 12 months. Therefore, the model was modified accordingly (Figure 10).

**Figure 10: Smoking Status Model (0 to 6 Months) for Assessing the Cost-Effectiveness of Paying or Copaying for Pharmacological Interventions**



It was further assumed in the model that there was no incidence of smoking-related disease during the first six months after the intervention. The initial age was set at 40 years, which was approximately equivalent to the baseline mean age that was reported in Kaper et al.<sup>195</sup> The probability of smoking cessation intervention use ( $P_S$ ) and quit rate (with the use of any cessation interventions:  $P_Q$ ) and the relative risk of smoking cessation use ( $rr_S$ ) and quit rate ( $rr_Q$ ) appear in Table 3. In the pay or co-pay model, the smoking status model 12 months after intervention (Figure 8) represents the smoking status at six months after the intervention.

### **Modelling the cost-effectiveness of treating specific patient populations**

For the analysis relating to patients with cardiovascular or smoking-related diseases and for hospitalized patients, the initial distribution of cohorts in each health state was modified to represent the new patient populations. In the the analysis relating to the general population, our initial assumption was that, at the beginning of the model, all members of a cohort were in the “No morbidity” state. However, this was not the case for specific populations; instead, everyone started with one of the morbidity states.

For patients with cardiovascular or smoking-related diseases, the initial cohort size of each chronic condition state was determined based on the patient characteristics that were reported in three studies<sup>96,121,179</sup> from which clinical efficacy was obtained. Because only Tonstad et al.<sup>179</sup> provided patient characteristics by health states, the authors of this report calculated the initial cohort size based on the distribution of morbidity status that was reported by Tonstad et al. In Tonstad et al., a total of 626 participants were randomized to receive bupropion or placebo. Among these participants, 49%, 33%, and 35% of them had MI, PVD, and angina, respectively (comorbidities were allowed). In addition, it was reported that 15.2% of them had COPD. Because our Markov models do not consider co-morbidities, we identified proportions based on the hierarchical order of disease progression: angina (assumed to represent CHD), PVD-AAA, then MI. Using this hierarchy, we assumed that 49% of the total participants had MI, and 33% of the total participants had PVD-AAA, and the remaining 18% ( $=100\% - 49\% - 33\%$ ) had CHD. We further assumed that the proportion of those with COPD (15.2%) was the same for all MI, PVD-AAA, and CHD groups. Based on this assumption, the proportion of those with MI, PVD-AAA, and CHD who also had COPD were calculated as 7.4% ( $= 0.49 * 0.152$ ), 5% ( $= 0.33 * 0.152$ ), and 2.7% ( $= 0.18 * 0.152$ ) respectively. Therefore, it was assumed that those with MI, PVD-AAA, and CHD without COPD were 41.6% ( $= 49\% - 7.4\%$ ), 28% ( $= 33\% - 5\%$ ), and 15.3% ( $= 18\% - 2.7\%$ ) respectively. These were initial cohort sizes in the chronic condition model; namely, if we consider a total cohort size of one at the beginning of the model, this was distributed to 12 health states: PVD-AAA = 0.280, CHD = 0.153, MI = 0.416, and COPD = 0.152 (the initial cohort size of other states was zero). Based on the baseline characteristics of the patient population reported by Tonstad et al., the authors of this report assumed 55 years to be the age at intervention.

For hospitalized patients, the chronic condition model was also modified so that it reflects the baseline distribution of chronic conditions that were reported in the included studies. The baseline characteristics of participants in Campbell *et al.*<sup>71</sup> were unclear. Therefore, we used the patient characteristics that were described in Rigotti *et al.*<sup>170</sup> to identify the initial size of the cohort in each chronic condition health state. In Rigotti *et al.*, of a total of 248 participants who were randomized to receive bupropion or placebo, 120 had a discharge diagnosis of MI, 102 had unstable angina, 14 had PVD, and the remaining 14 had other cardiovascular diseases. Therefore, of a total of 236 participants who had a discharge diagnosis of MI, unstable angina, or PVD, we

calculated the proportion of those with MI, CHD (unstable angina was a proxy), and PVD to be 51.1% (= 120/236), 43.2% (= 102/236), and 5.8% (= 14/236) respectively. Namely, the chronic condition model (Figure 9) begins with the following distribution of cohorts (assuming a total initial cohort size of one): PVD-AAA = 0.058, CHD = 0.432, and MI = 0.511 (the initial cohort size of other states was zero). The baseline mean age of study participants reported in Rigotti *et al.*<sup>170</sup> was approximately 56 in the bupropion and placebo groups. Therefore, we set 56 years as the age at intervention.

### **Model validation**

Internal validation of the model was carried out to ensure that any errors in programming were resolved and that the calculations of model parameters were accurate. External validation was conducted by comparing the mortality that was predicted by using our model with the all-cause mortality of smokers and quitters that was derived from the life table using the base-case model for the general population. For both smokers and quitters, the authors of this report calculated undiscounted and discounted (at an annual rate of 5%) life expectancy at the age of 20 years. These model-predicted life expectancies were compared with the actual life expectancies that were calculated from the age, gender, and smoking-specific death rates (shown in Appendix 15, Table A14). The comparisons of model-predicted and actual life expectancies showed that our base-case model predicted higher mortality than was actually observed. Therefore, we assumed that the mortality from diseases not included in the model and the rate of change in this mortality rate by age in smokers and quitters were the same as those for never smokers after the age of 30 years. Nonetheless, discrepancies between actual and predicted survival existed in our model. After adjusting for all-cause mortality rates of smokers and quitters, the discounted differences between actual and predicted life expectancies were 0.9 years and 1.2 years among male and female smokers respectively, and 0.9 years for quitters.

### **5.3.8 Valuing outcomes**

The outcomes considered in our model were the number of additional quitters, LY gained, and QALYs gained. LYs were weighted by utilities for each chronic health state to obtain QALYs. A search for the utility scores of each chronic condition state was done by a review of literature (based on MEDLINE search, Cost Effective Analyses Registry Database,<sup>243</sup> and handsearches), and the data analyses of Canadian population health survey data. When selecting the utility scores for each health state, utilities that were representative of the Canadian general population derived from a common elicitation method/instrument, and/or based on a large sample size, were preferred.

Our search results showed that no single instrument adequately met our criteria, and not all utility scores for health states considered were based on a Canadian general population. Therefore, the utility scores were obtained from several sources. The utilities for no morbidity, CHD, and COPD were based on the data analyses using Canadian Community Health Survey (CCHS) Public Use Microdata Files (PUMF).<sup>252</sup> The utilities for PVD, stroke, post-stroke, MI, and post MI states were based on a catalogue of utility scores that were estimated from a sample of the US general population.<sup>253,254</sup> The utilities for TIA, lung cancer, and asthma exacerbation were based on published articles.<sup>255-257</sup> We considered the utility score of the post TIA state to be equivalent to that of the no morbidity state, assuming that a utility decrement due to a TIA event will be minimal after one year of no further incidence of TIA. Table 6 lists the utility

scores that were used in our analyses. Appendix 16 also describes the methods in the data analyses using CCHS PUMF.

Table 6: Utilities for Health States				
Health State	Mean (SE)*	Distribution <sup>†</sup>	Instrument	Source
No morbidity	Appendix 17 <sup>†</sup>	Lognormal	HUI3	CCHS 3.1. <sup>252</sup>
PVD-AAA	0.734 (0.006)	Lognormal	EQ-5D	Sullivan et al. <sup>253</sup>
Stroke	0.650 (0.014)	Lognormal	EQ-5D	Sullivan and Ghushchyan <sup>254</sup>
Post-stroke	0.694 (0.005)	Lognormal	EQ-5D	Sullivan et al. <sup>253</sup>
TIA	See Appendix 17 <sup>†</sup>	Lognormal	HUI3	Haacke et al. <sup>255</sup>
Post-TIA	Assumed to be same as No morbidity state	Lognormal	n/a	n/a
MI	0.704 (0.013)	Lognormal	EQ-5D	Sullivan and Ghushchyan <sup>254</sup>
Post-MI	0.725 (0.003)	Lognormal	EQ-5D	Sullivan et al. <sup>253</sup>
CHD	Appendix 17 <sup>†</sup>	Lognormal	HUI3	CCHS 3.1. <sup>252</sup>
COPD	Appendix 17 <sup>†</sup>	Lognormal	HUI3	CCHS 3.1. <sup>252</sup>
Lung cancer	0.580 for male 0.670 for female	Lognormal	EQ-5D	Trippoli et al. <sup>256</sup>
Asthma exacerbation	See Appendix 17 <sup>†</sup>	Lognormal	EQ-5D	Bond et al. <sup>257</sup>
Death	0.00	n/a		Defined

\*Standard errors for PVD-AAA, stroke, post stroke, MI, and post-MI were calculated based on mean, sample size, and 25% and 75% percentiles reported in Sullivan et al.<sup>253,254</sup>

<sup>†</sup>Utility scores for these states depend on age, gender, and/or smoking status; See Appendix 17 for further details.

<sup>†</sup>Uncertainties regarding utilities (U) were assessed around disutilities:  $\bar{U} (= 1 - U)$ , assuming a lognormal distribution. To ensure that the back transformation of the natural log of disutility scores returns to means, uncertainties were assessed assuming the normal distribution around  $\ln(\bar{U})$  with mean of  $\ln(\bar{U}) - \frac{1}{2}(\ln(1 + \frac{SE(U)^2}{U^2}))$  and the standard deviation of  $\sqrt{\ln(\frac{SE(U)^2}{U^2} + 1)}$ .

where SE(U) refers to standard error of utility estimate. The resulting estimate of  $\ln(\bar{U})$  was exponentiated and subtracted from 1 to obtain the utility score (U).

### 5.3.9 Resource use and costs

Two types of costs were used in our economic model: intervention costs and morbidity costs. The intervention costs that were considered were the cost of pharmacological interventions (i.e., NRT [various types], bupropion, and varenicline) and behavioural intervention, if applicable. The costs of morbidity considered were the costs associated with treating chronic conditions such as testing, hospitalization, surgery, medications, and other relevant direct health care costs.

**a) Intervention cost**

Because the dosages of pharmacological interventions were often trial-specific, intervention costs were identified for each of the five models separately. In the economic model targeting a general population, the standard dosage information for each pharmacological intervention was identified from e-CPS, and these dosages were assumed in the model.<sup>258</sup> Table 7 shows the dosage and unit cost of pharmacological interventions in the general population model.

Dispensing fees were calculated based on the assumption that (unless otherwise noted), when each prescription was filled, a four-week supply was dispensed. In other models, the dosage and duration was adjusted to reflect those that were used in the included trials. Appendix 18 shows the intervention costs that were used in models other than the general population model.

In calculating the costs of pharmacological interventions, the full cost (drug cost, dispensing fee, markups, and inventory allowance) was considered in the base-case scenario. The dispensing fee, wholesale markups, inventory allowance, and copayment were based on Alberta Health and Wellness.<sup>259,260</sup> In the deterministic sensitivity analyses, the cost to the drug plan was reduced by including patient copayment.<sup>232</sup> We considered sources from Alberta to identify these charges because a number of drugs that were considered in our reports were covered in Alberta, and the drug prices and relevant up-charges were available publicly. If the costs of drugs were obtained from sources other than the Alberta formulary, it was assumed that the same up-charges applied to these drugs.

**Table 7: Intervention Costs Used for Models for the General Population (2008 Canadian Dollars)\***

Name [Strength]	Dosage <sup>†</sup>	Duration (# of Prescriptions)	Unit Cost	Total Cost <sup>‡</sup>	Source
<b>Nicotine gum</b> [2 mg or 4 mg]	11 pieces per day in weeks 1 to 4; 4 pieces per day in weeks 5 to 8; 2 pieces per day in weeks 9 to 12	12 weeks (3)	\$0.3130 (2 mg for low dependence) <sup>§</sup>  \$0.3793 (4 mg for high dependence)	\$193 for 2 mg  \$227 for 4 mg	Alberta Health and Wellness <sup>261</sup>
<b>Nicotine patch</b> [7 mg, 14 mg or 21mg]	21 mg in weeks 1 to 6; 14 mg in weeks 7 to 8; 7 mg in weeks 9 to 10	10 weeks (3) <sup>††</sup>	\$2.6786 (Habitrol)  \$3.4771 (Nicoderm)	\$248 (for Habitrol) <sup>**</sup>  \$308 (for Nicoderm) <sup>**</sup>	Alberta Health and Wellness <sup>261</sup>
<b>Nicotine inhaler</b> [10 mg cartridge]	9 cartridges per day for 12 weeks	12 weeks (3)	\$0.75	\$687	Alberta Health and Wellness <sup>261</sup>
<b>Nicotine lozenge</b> [2mg or 4mg]	10 pieces per day in weeks 1 to 6; 7 pieces per day in weeks 7 to 9; 3 pieces per day in weeks 10 to 12	12 weeks (3)	\$0.415 (for 2 mg) <sup>§</sup> \$0.4742 (for 4 mg)	\$327 (for 2 mg)  \$367 (for 4 mg)	Johnson & Johnson Inc.

**Table 7: Intervention Costs Used for Models for the General Population (2008 Canadian Dollars)\***

Name [Strength]	Dosage <sup>†</sup>	Duration (# of Prescriptions)	Unit Cost	Total Cost <sup>‡</sup>	Source
<b>Varenicline</b> [0.5 mg or 1 mg]	0.5 mg per day on days 1 to 3; 0.5 mg twice daily on days 4 to 7; 1 mg twice daily thereafter	12 weeks (4)	2-week starter pack (11 0.5 mg tablets and 14 1 mg tablets) = \$42.13  2-week consultation pack (28 1 mg tablets) = \$47.18 <sup>††</sup>	\$304	Pfizer Inc.
<b>Bupropion</b> [150 mg]	150 mg per day for 3 days; 150 mg twice daily thereafter	12 weeks (3)	\$0.9191	\$196	Alberta Health and Wellness <sup>261</sup>

\*All the intervention costs were considered as deterministic; drug prices were based on data available in 2009. However, we assumed these prices to be equivalent to the 2008 prices because of the absence of the 2009 consumer price indices.

<sup>†</sup> For Nicotine gum, inhaler, and lozenge, a midpoint of recommended dosage provided in e-CPS was used. For Nicotine patch, the authors of this report considered the most frequently observed dosage option based on a review of included clinical trials in our report and expert opinion.

<sup>‡</sup>In the base-case scenario, full cost (drug cost, dispensing fee, wholesale markups, inventory allowance) was considered. Dispensing fee, wholesale markups, inventory allowance, and copayment were based on Alberta Health and Wellness.<sup>259,260</sup> In the deterministic sensitivity analyses, cost to the drug plan was reduced by including patient copayment.

<sup>§</sup>In the base-case scenario, high dependence case was considered. In the deterministic sensitivity analyses, low dependence case was considered.

<sup>¶</sup>Assuming that the first two prescriptions were filled every four weeks and the third prescription was filled for weeks nine to 10.

<sup>\*\*</sup>Based on private insurance claim data provided by Brogan Inc., Nicoderm patch was the most frequently claimed brand in 2007-2008 (Source: Brogan Inc. Public and Private Drug Plan Databases). Therefore, the price of the Nicoderm patch, which was the highest-priced option among nicotine patches in Alberta Health and Wellness formulary, was used in a base-case scenario. In a sensitivity analysis, the unit cost of Habitrol, the lowest-priced option, was used.

<sup>††</sup> First prescription consists of one 2-week starter pack (0.5 mg tablet once daily on days 1 to 3; 0.5 mg tablet twice daily on days 4 to 7; 1 mg tablet twice daily on days 8 to 14), then the second and the third prescriptions consist of two 2-week consultation packs (1 mg twice daily for 2 weeks per pack) for each prescription, then the final prescription consists of one 2-week consultation pack.

### **b) Morbidity cost**

The annual direct costs of smoking-related morbidities were obtained from a review of published articles. All the cost data were based on Canadian sources. Whenever necessary, the costs from various years were adjusted to 2008 Canadian dollars using Canadian consumer price indices.<sup>262</sup>

A list of morbidity costs and their sources appears in Appendix 19.

The annual direct treatment costs of CHD (cost of angina as a proxy of CHD cost), stroke, post-stroke, MI, and post-MI states were based on physician billing or hospital discharge records of approximately 5 million residents in Ontario.<sup>263</sup> The direct treatment costs of TIA were based on a six-month prospective study of all patients presenting with TIA to the emergency room of hospitals in Hamilton, Ontario.<sup>264</sup> The authors of this report assumed that there is no treatment cost associated with the post TIA state, considering that TIA lasts for a few hours to a day and does not incur any treatment cost in subsequent years after the TIA event. The costs of PVD-AAA were based on two sources. The PVD costs were determined as the weighted average of inpatient and ambulatory PVD costs based on 2006 Alberta health cost data,<sup>265</sup> and the costs of

AAA were based on Ontario Case Costing Initiative (OCCI).<sup>266</sup> The costs that were included in OCCI were direct and indirect costs associated with acute inpatient and ambulatory care of AAA (with or without rupture). The costs of COPD were based on a self-reported survey of a random sample of 401 Canadians with COPD.<sup>267</sup> The costs of lung cancer were calculated as a weighted average cost of small-cell (limited and extensive) and non-small-cell (all stages) lung cancers that were obtained from a chart review of 512 incident cases of primary lung cancer in Alberta.<sup>268</sup> The costs of asthma exacerbation were based on a weighted average of general practitioner-managed, emergency room visit, and hospitalization asthma exacerbation costs.<sup>257</sup> Because asthma exacerbation was treated as an acute event, the total expected cost of asthma exacerbation at each cycle was calculated by multiplying the following three elements:

- the per-patient cost of asthma exacerbation
- the total number of patients alive at each cycle
- the probability of asthma exacerbation.

This amount was added as the total costs in each cycle.

### 5.3.10 Discount rate

For costs and outcomes occurring beyond the first year, a 5% annual discounting rate was used as a base-case scenario.<sup>232</sup> Zero and 3% annual rates were used for sensitivity analyses.

### 5.3.11 Variability and uncertainty

Our research questions reflected the assessment of population heterogeneity (e.g., by age, gender, smoking status, chronic conditions) by assessing potential difference in cost-effectiveness of alternative smoking cessation interventions among various population subgroups. Therefore, a separate set of Markov models was run for the general population and specific populations, based on the availability of clinical evidence.

The model parameter uncertainty was assessed using deterministic sensitivity analyses and probabilistic analyses. The decision uncertainty was assessed using value of information analyses. Each of the methods is described in detail below.

#### a) **Deterministic sensitivity analyses**

Deterministic sensitivity analyses were conducted for the following parameters:

- Discount rates
  - 0% and 3% for costs and outcomes were assessed instead of the base-case rate of 5%
- Parameters associated with clinical efficacy
  - PPA at 12 months
  - PPA at 6 months
  - CAR at 6 months
- Placebo quit rates instead of spontaneous quit rates
- Intervention costs
  - NRT patch price
    - The cost of Habitrol (unit cost of \$2.6786, the lowest price option) was used instead of the cost of Nicoderm (unit cost of \$3.4771, the highest price option).
- Patient copayment

- An inclusion of 30% patient copayment to the total cost of pharmacological interventions
- Dosage of lozenge and/or gum
  - Low dosage (i.e., low cost) of lozenge and/or gum (2 mg instead of 4 mg) was assumed.

In the analysis assessing the cost-effectiveness of adding behavioural interventions, the following assumptions were also assessed:

- Length of telephone counselling
  - In Lando et al.,<sup>125</sup> the telephone counselling time varied between 10 and 15 minutes. Therefore, a 10-minute call was assumed instead of the base-case of 15 minutes per call.
- Cost of telephone counselling
  - The base-case analysis was conducted using the rate at 32.5 cents per minute as the cost of telephone counselling (Gail Luciano, Canadian Cancer Society, Hamilton, ON: personal communication, 2009 September 30). It was also reported that, in British Columbia, telephone smoking cessation counselling costs approximately \$30 per call, usually lasting for about 15 to 30 minutes per call (Frankie Best, Ministry of Healthy Living and Sport, Victoria, BC: personal communication, 2009 October 5). This is equivalent to approximately \$1.33 per minute. Therefore, the British Columbia rate was used.

In the analysis assessing cost-effectiveness targeting those with cardiovascular or other smoking-related diseases, the following assumption was also assessed:

- Treatment duration
  - In the trial that the efficacy data was obtained,<sup>121</sup> interventions of NRT patch and inhaler lasted up to nine months. Therefore, a treatment duration of nine months for NRT patch and inhaler was assumed.

#### **b) Probabilistic analyses**

Monte Carlo simulation (MCS) was conducted to assess parameter uncertainty in a more comprehensive manner by specifying a priori distributional assumptions for each uncertain input parameter. In our model, clinical efficacy (quit rates), long-term relapse rates, transition probabilities, morbidity costs, utilities, relative risks of developing smoking-related morbidities, and selected drug costs were subject to probabilistic analyses. Distributional assumptions were specified in previous sections. A preliminary investigation was conducted to determine the optimal number of iterations to be conducted for Monte Carlo simulation (MCS). The authors of this report compared the results of MCS based on 1,000, 2,000, 3,000, 5,000, 7,000, and 10,000 iterations for each model. Visual assessment showed that, in general, little information was added after 5,000 iterations. Therefore, the number of iterations was set at 5,000 for each model.

The results of MCS were summarized using cost-effectiveness acceptability curves (CEAC) representing the probability of an intervention to be cost-effective for a range of cost-effectiveness threshold levels.

**c) Value of information analyses**

Following MCS, value of information (VOI) analyses were conducted.<sup>236</sup> A VOI analysis quantifies the expected cost (or opportunity loss) of an incorrect decision made based on currently available but uncertain information. The objectives of the VOI analyses pursued were to calculate:

- the expected overall value of information based on current (imperfect) information
- the expected value of information of each (set of) uncertain parameter(s).

In each model, we conducted expected value perfect information (EVPI) and expected value of perfect partial information (EVPPI) analyses to assess each objective respectively.

EVPI is used to estimate the overall opportunity loss that is associated with all the uncertain parameters in the model. The results of EVPI are used to inform decision-makers about the value of reducing all the parameter uncertainty in the model and whether further research is worthwhile. EVPPI is used to estimate which parameter(s) contribute more than others to the overall uncertainty in a model and the values that are associated with reducing the uncertainty. The results of EVPPI are useful in setting specific future research priorities by identifying parameters that are likely to provide value for obtaining additional information to reduce decision uncertainty.

EVPI was obtained using results from MCS for the base analysis only. The calculation of EVPPI is similar to that of EVPI, but involves more complex computational steps. Coyle and Oakley<sup>270</sup> reviewed five methods for estimating EVPPI. In our report, our objective of VOI analyses was to assess the degree of contribution of each (or set of ) parameter(s) with respect to the overall decision uncertainty, not to address further the optimal study design, duration, or sample size (i.e., expected value of sample information). Therefore, similar to a previous analysis,<sup>271</sup> single-stage MCS was used in our analyses to minimize computational burden without compromising the accuracy of our study implications. This was done by assessing EVPI by setting a parameter (or a set of parameters) of interest to be probabilistic, holding other parameters at their deterministic values.

The authors of this report assessed EVPPI for a group of parameters in a way that is informative to policy-makers. Namely, clinical efficacy (quit rate) was assessed together so that further information could be obtained from additional trials. Similarly, long-term relapse rates, morbidity costs, utilities, relative risks of smoking-related morbidities, and disease transition probabilities were assessed as separate parameter groups.

**d) Equity**

In our analysis, our research questions address implications of varying cost-effectiveness across demographic and disease-specific groups. More specifically, the cost-effectiveness and decision uncertainty were assessed for age-, gender-, and disease-specific populations (i.e., those with cardiovascular or smoking-related chronic disease and hospitalized populations).

## 5.4 Primary Economic Evaluation: Results

We conducted cost-effectiveness analyses targeting general populations (by age and gender), specific populations (those with cardiovascular or other smoking-related diseases and hospitalized patients), adding behavioural interventions and payment or copayment of pharmacological interventions. Base-case results, uncertainty analyses, and value of information analyses are presented separately for each analysis.

### 5.4.1 Among the general population of smokers, what is the cost-effectiveness of varenicline compared with that of bupropion and that of NRT?

#### a) *Base-case analysis and results*

The base-case results for males aged 20 years for the primary cost utility analysis is presented in Table 8. Secondary analyses based on cost per LY gained, and costs per additional quitter are detailed in Tables 9 and 10. Summary results for other age-gender cohorts are provided in Table 11. More detailed results are provided in Appendix 20.

For the base case analysis for males aged 20 at age of intervention, NRT gum and patch were dominated by bupropion and NRT patch, lozenge and inhaler were dominated by varenicline. Varenicline had higher costs and QALYs (\$5,698; 14.395) than no intervention (\$5,405; 14,362) and bupropion (\$5,566; 14.380). The incremental cost per QALY gained for varenicline versus no intervention was \$9,083. The incremental cost per QALY gained for varenicline versus bupropion ranged from \$9,107.

Regardless of age and gender, nicotine gum, patch, lozenge, and inhaler showed higher lifetime costs and lower QALYs (and LYs and quitters) compared with at least one of bupropion and varenicline (Tables 9, 10, 11 and Appendix 20). For all cohorts, varenicline had higher costs and more QALYs than no intervention and bupropion. The incremental cost per QALY gained for varenicline versus no intervention ranged from \$4,148 to \$10,236. The incremental cost per QALY gained for varenicline versus bupropion ranged from \$4,164 to \$10,265. Thus, as long as a decision maker was willing to spend at least \$10,265 per QALY gained, varenicline was cost effective in all cohorts.

In summary, for the general population, as long as a decision maker was willing to spend at least \$10,265 per QALY gained, varenicline was the optimal treatment choice compared to NRT (patch, gum, lozenge and inhaler) and bupropion.

**Table 8: Results of Primary Analysis - Male aged 20 years**

Intervention	QALYs	Cost	Incremental Cost per QALY gained vs. no intervention	Incremental Cost per QALY gained (sequential)*
No intervention	14.362	\$5,405	---	---
Bupropion	14.380	\$5,566	\$9,063	\$9,063
Varenicline	14.395	\$5,698	\$9,083	\$9,107
<b>Dominated therapies</b>				
Gum	14.376	\$5,599	\$14,784	Dominated

**Table 8: Results of Primary Analysis - Male aged 20 years**

Intervention	QALYs	Cost	Incremental Cost per QALY gained vs. no intervention	Incremental Cost per QALY gained (sequential)*
Patch	14,377	\$5,670	\$17,821	Dominated
Lozenge	14.387	\$5,715	\$12,505	Dominated
Inhaler	14.386	\$6,007	\$25,586	Dominated

\*Sequential analysis reports results on the cost effectiveness frontier (i.e. bupropion versus no intervention and varenicline versus bupropion). All other therapies are dominated.

**Table 9: Results of Secondary Analysis (life years gained) - Male aged 20 years**

Intervention	LYs	Cost	Incremental cost per life year gained (vs. no intervention)	Incremental cost per life year gained (sequential)*
No intervention	16.192	\$5,405	---	---
Bupropion	16.200	\$5,566	\$19,244	\$19,244
Varenicline	16.207	\$5,698	\$19,285	\$19,226
<b>Dominated therapies</b>				
Gum	16,198	\$5,599	\$31,391	Dominated
Patch	16.199	\$5,670	\$37,840	Dominated
Lozenge	16.203	\$5,715	\$26,551	Dominated
Inhaler	16.203	\$6,007	\$54,327	Dominated

\*Sequential analysis reports results on the cost effectiveness frontier (i.e. bupropion versus no intervention and varenicline versus bupropion). All other therapies are dominated.

**Table 10: Results of Secondary Analysis (quitters) - Male aged 20 years**

Intervention	Proportion who quit	Cost	Incremental cost per quitter (vs. no intervention)	Incremental cost per quitter (sequential)*
No intervention	0.034	\$0.02	---	---
Bupropion	0.064	\$12.50	\$421	\$421
Varenicline	0.088	\$31.26	\$582	\$779
<b>Dominated therapies</b>				
Gum	0.056	\$12.70	\$581	Dominated
Patch	0.059	\$18.12	\$730	Dominated
Lozenge	0.075	\$27.69	\$670	Dominated
Inhaler	0.073	\$50.34	\$1,285	Dominated

\*Sequential analysis reports results on the cost effectiveness frontier (i.e. bupropion versus no intervention and varenicline versus bupropion). All other therapies are dominated.

**Table 11: Results of Primary Analysis for Age-Sex Cohorts**

Cohort	Incremental Cost per QALY gained*		
	Bupropion vs. no intervention	Varenicline vs. no intervention	Varenicline vs, Bupropion
<b>Males</b>			
aged 20 years	\$9,063	\$9,083	\$9,107
aged 30 years	\$10,212	\$10,236	\$10,265
aged 40 years	\$6,700	\$6,717	\$6,738
aged 50 years	\$10,114	\$10,143	\$10,178
aged 60 years	\$4,136	\$4,148	\$4,164
<b>Females</b>			
aged 20 years	\$9,579	\$9,599	\$9,625
aged 30 years	\$9,139	\$9,161	\$9,187
aged 40 years	\$5,547	\$5,562	\$5,580
aged 50 years	\$4,944	\$4,958	\$4,976
aged 60 years	\$6,058	\$6,077	\$6,100

\*All other therapies are dominated.

### **b) Results of uncertainty analyses**

#### **Sensitivity analyses**

Appendix 21 shows clinical efficacy data that were used in the sensitivity analyses. Appendix 22 shows results from a series of sensitivity analyses - only the results for ages at intervention of 20 years and 40 years are presented (complete results are available upon request). The results were only found to be sensitive to the definition of quit rates. When the definition of PPA at 12 months was used as a quit rate, bupropion and varenicline were dominated by lozenge. When PPA at six months was used, varenicline dominated bupropion by extended dominance. When CAR at six months was used, gum and varenicline dominated bupropion by extended dominance.

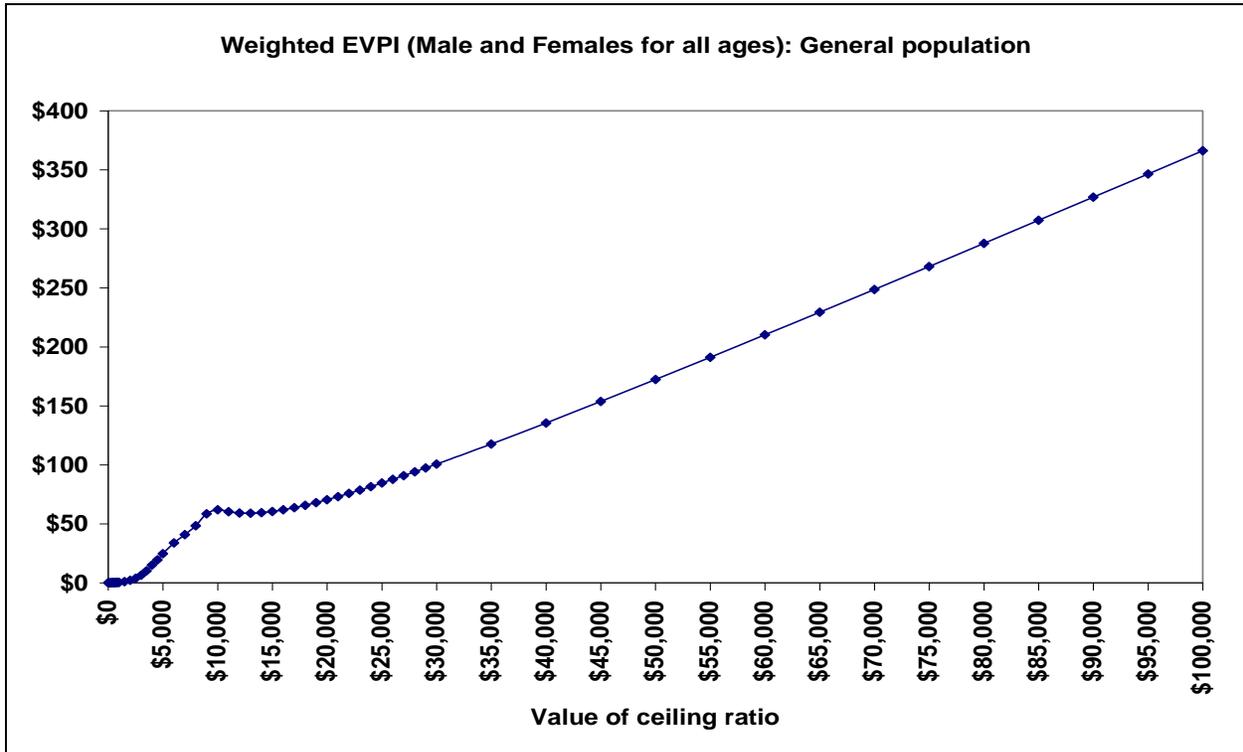
#### **Monte Carlo simulation**

The results from the MCS are summarized in CEACs by age at intervention and gender (Appendix 23). Assuming a decision maker was willing to pay at least \$10,000 for a QALY; varenicline was optimal and had the highest probability of being cost effective.

### **c) Results of value of information analysis**

EVPI was estimated by weighted cohort estimates of EVPI by the prevalence of smokers who attempt to quit smoking by age and gender (see Appendix 24 for detailed information on the calculation of weights). It was estimated that the total number of daily smokers in Canada aged 15 years and older who made at least one quit attempt in the past 12 months was approximately 1,762,000.<sup>272</sup> Using this estimate, the authors of this report calculated per person and population EVPI for various threshold levels (Table 12). Figure 11 shows EVPI by the threshold value for QALY. At a value of a QALY of \$50,000, the weighted EVPI was \$172 per person and the population EVPI was \$295 million. The age- and gender-specific results of per person EVPI appear in Appendix 25.

**Figure 11: Weighted EVPI for General Population**



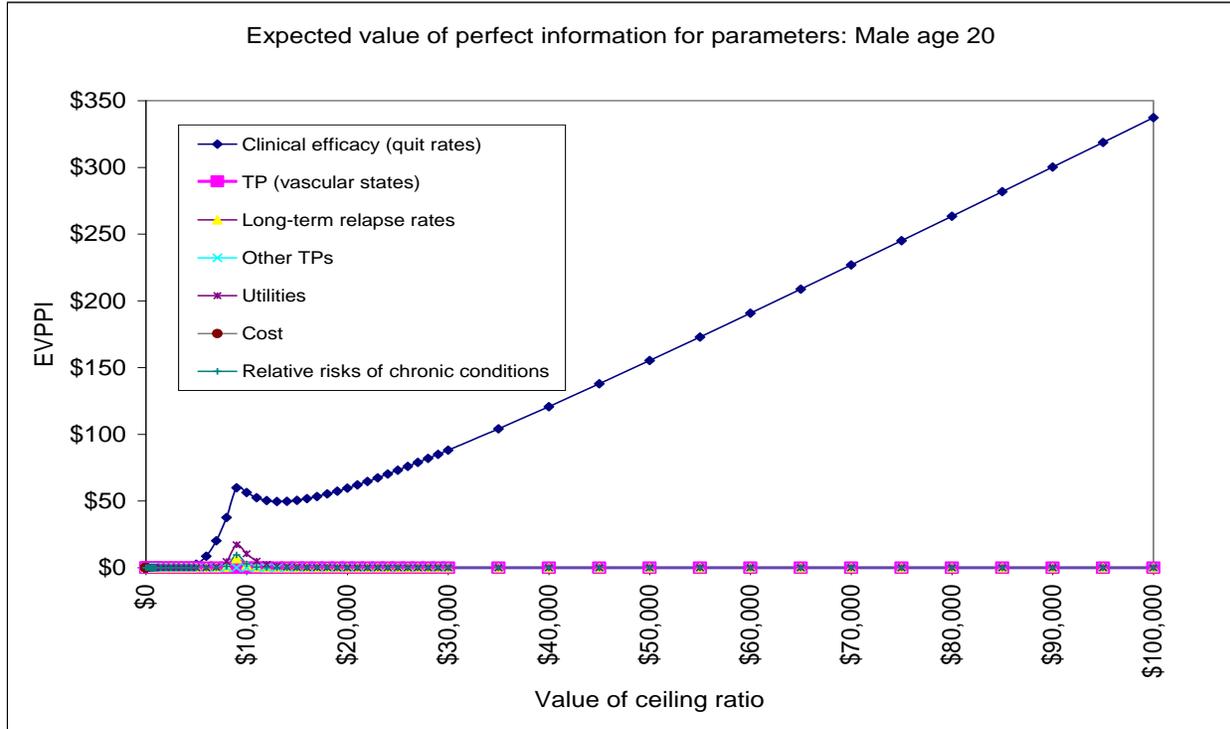
EVPI = expected value of perfect information.

Threshold	Per Person Weighted EVPI	Population Weighted EVPI (In Millions)
\$5,000	\$25	\$43
\$10,000	\$62	\$106
\$30,000	\$101	\$173
\$50,000	\$172	\$295

EVPI = expected value of perfect information.

The results of the EVPPI analyses are presented in Figure 12. A group of parameters representing clinical efficacy (i.e., quit rates) showed the greatest EVPPI among all the stochastic parameters regardless of the threshold value of a QALY. This indicates that most of the decision uncertainty resulted from uncertainties around quit rates that were associated with pharmacological interventions. Further EVPPI analyses showed that, in males and females, most of the decision uncertainty around quit rates was attributable to that of lozenge, inhaler, and varenicline (results not shown). Therefore, further research assessing the efficacy of pharmacological interventions would provide the greatest information values among all the stochastic parameters in reducing decision uncertainty.

**Figure 12: EVPPI (General Population)**



EVPPI = expected value of perfect partial information; TP = transition probability.

**5.4.2 Among the general population of smokers using varenicline, or bupropion or NRT, what is the cost-effectiveness of adding a behavioural support program to drug therapy?**

**a) Base-case analyses and results**

The base-case analyses showed that a strategy of adding 15-minute telephone counselling by a counsellor to nicotine patch therapy was not cost effective as it was more costly and resulted in less QALYs (and LYs and quitters) (Table 13).

Table 13: Base-Case Results					
Cost per QALY gained					
Intervention	QALYs	Cost	Incremental QALYs (vs. patch)	Incremental Cost (vs. patch)	ICER
<b>Male</b>					
Patch	11.603	\$12,102	---	---	---
Patch+Behaviour	11.600	\$12,126	-0.003	\$24	Dominated
<b>Female</b>					
Patch	11.917	\$12,806	---	---	---
Patch+Behaviour	11.913	\$12,831	-0.004	\$25	Dominated

ICER = incremental cost-effectiveness ratio;; QALY = quality-adjusted life-year; vs. = versus.

## **b) Results of uncertainty analysis**

### **Sensitivity analyses**

The results of sensitivity analyses (Appendix 26) indicated that the results were robust with respect to patient copayment, patch price, discount rates, cost of counselling, and duration of counselling.

### **Monte Carlo simulation**

For males and females, the probability of patch therapy alone being cost-effective was consistently greater than that of the combination therapy of patch and telephone counselling although the probability of counselling being cost effective was approximately 40% for all values of a QALY above \$10,000 (Appendix 27). This highlights the degree of uncertainty within this analysis.

### **In summary**

Analysis of the cost effectiveness of adding behavioural support to a cessation intervention was limited to consideration of NRT patch. Analysis found that adding behavioural support to NRT patch was not cost effective as it increased costs and led to fewer QALYs.

## **5.4.3 What is the impact of copayment (of insurance claim) or payment (i.e., purchase drug as over-the-counter product) on the cost-effectiveness of drugs used for smoking cessation therapy?**

### **a) Base-case analysis and results**

The base-case analysis of the cost-effectiveness of full reimbursement versus no reimbursement for NRT and bupropion showed that the full reimbursement of the pharmacotherapy resulted in greater benefits (in QALYs, LYs, and the number of quitters), with higher costs (Table 14). Providing full benefits resulted in an additional 0.78 to 0.81 discounted QALYs gained per person, with an additional cost of \$787 to \$832. The ICERs were \$999 and \$1,026 per QALY gained.

<b>Table 14: Base-Case Results</b>					
<b>Cost per QALY Gained</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no reimbursement)</b>	<b>Incremental cost (vs. no reimbursement)</b>	<b>ICER</b>
<b>Male</b>					
No Reimbursement	0.494	\$447	---	---	---
Reimbursement	1.282	\$1,234	0.788	\$787	\$999
<b>Female</b>					
No Reimbursement	0.510	\$474	---	---	---
Reimbursement	1.321	\$1,306	0.811	\$832	\$1,026

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

## **b) Results of uncertainty analysis**

### **Sensitivity analyses**

Sensitivity analyses were conducted for nicotine patch price, gum dosage, and discount rates (Appendix 28). The results were found to be robust to all the parameters considered. Namely, the full reimbursement option resulted in greater costs and outcomes, with ICERs that were comparable to those in the base-case analyses.

### **Monte Carlo simulation**

The MCS results showed that the probability of full reimbursement option being cost-effective was 100% as long as a decision maker was willing to spend \$1,500 per QALY gained (Appendix 29).

### **In summary**

Analysis of reimbursement was limited to consideration of bupropion and NRT. Analysis found that providing full reimbursement of smoking cessation therapy was cost effective compared to no reimbursement as long as a decision maker was willing to spend at least \$1,026 per QALY gained.

## **5.4.4 Among smokers, what is the cost-effectiveness of treating specific patient populations with varenicline or bupropion or NRT, including a combination of these agents with behavioural support programs?**

### **a) Models for those with cardiovascular or smoking-related diseases**

The base-case results showed that, compared with no intervention, the use of bupropion resulted in more QALYs, LYs, and the number of quitters with additional costs (Table 15). The incremental costs per QALY gained for bupropion therapy compared with no intervention were \$3,312 and \$3,759, depending on gender. NRT (gum, patch, inhaler, or patch plus inhaler) was dominated by bupropion, generating fewer benefits in LYs, QALYs, and the number of quitters, and higher costs.

### **Sensitivity analysis**

Sensitivity analyses of varying patch price, duration of patch and inhaler therapies, adding patient copayment to the price of pharmacotherapies, discount rates, and use of CAR at six months as the definition of quit rates did not alter the implications provided in the base-case analyses (Appendix 30). For all cases, NRT was a dominated therapy among the three types of interventions, and the ICERs of bupropion (versus no intervention) were less than \$4,000 per QALY gained.

### **Monte Carlo simulation**

CEACs (Appendix 31) indicated bupropion showed the highest probability of being cost-effective as long as threshold value was greater than \$6,000.

<b>Table 15: Base-Case Results</b>						
<b>Cost per QALY Gained</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental Cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male</b>						
No intervention	4.744	\$27,363	---	---	---	---
Bupropion	4.792	\$27,522	0.048	\$159	\$3,312	\$3,312
<b>Dominated therapies</b>						
NRT*	4.789	\$27,894	0.044	\$531	\$11,976	Dominated
<b>Female</b>						
No intervention	5.354	\$28,418	---	---	---	---
Bupropion	5.389	\$28,551	0.035	\$133	\$3,759	\$3,759
<b>Dominated therapies</b>						
NRT*	5.386	\$28,925	0.033	\$507	\$15,483	Dominated

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; vs. = versus.

\*Patch, gum, inhaler, or patch plus inhaler interventions.

†The analyses were based on a one-year time horizon.

### ***In summary***

Analysis of the cost effectiveness of cessation interventions for cardiovascular patients was restricted to bupropion and NRT (gum, patch, inhaler, or patch plus inhaler). As long as a decision maker was willing to spend at least \$3,759 per QALY gained, bupropion was the optimal treatment choice,

### ***b) Models for hospitalized patients***

The cost-effectiveness of pharmacological interventions was assessed for three interventions: no intervention, bupropion, and nicotine patch. The base-case results indicated that, compared with no intervention, bupropion and patch options resulted in greater QALYs (and LYs and the number of quitters), with additional cost (Table 16). Patch was more costly and more effective than bupropion. The incremental cost per QALY gained for bupropion versus no intervention was \$7,658 for males and \$10,143 for females. The incremental cost per QALY gained for patch versus bupropion was \$86,406 for males and \$121,675 for females. Thus, if a decision maker is willing to pay at least \$10,000 and no more than \$80,000 for a QALY, bupropion would be the optimal treatment.

### ***Sensitivity analysis***

For all the parameters that were assessed, the results of sensitivity analyses (Appendix 32) were consistent with those of the base-case analysis that bupropion was the most cost-effective option compared with no intervention, followed by NRT patch.

### ***Monte Carlo simulation***

CEACs (Appendix 33) indicated that, for a threshold greater than \$10,000 per QALY gained, the probabilities of patch and bupropion being cost-effective were similar.

**Table 16: Base-Case Results**

Cost Per QALY Gained						
Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male</b>						
No intervention	4.616	\$28,000	---	---	---	---
Bupropion	4.643	\$28,206	0.027	\$207	\$7,658	\$7,658
Patch	4.645	\$28,363	0.029	\$364	\$12,624	\$86,406
<b>Female</b>						
No intervention	5.245	\$28,893	---	---	---	---
Bupropion	5.264	\$29,086	0.019	\$193	\$10,143	\$10,143
Patch	5.266	\$29,242	0.020	\$349	\$17,177	\$121,675

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

### *In summary*

Analysis of the cost effectiveness of cessation interventions for hospitalized patients was restricted to bupropion and NRT patch. If a decision maker was willing to spend at least \$10,143 per QALY gained, bupropion was the optimal treatment choice. However, if a decision maker was willing to spend more than \$86,406 per QALY gained, NRT patch may be cost effective.

## **6 HEALTH SERVICES IMPACT**

### **6.1 Population Impact**

In 2008, the estimated number of daily and occasional smokers in Canada was approximately 4.9 million (18% of the population aged 15 years or older), which was a decline from the approximately 6.1 million smokers (25% of the population aged 15 years or older) in 1999.<sup>276</sup> The prevalence of smokers has been declining over time. Approximately 35% of the total population were smokers in 1985. The prevalence declined to approximately 32% in 1994-1995, 24% in 2000, and 19% in 2005.<sup>276</sup> The prevalence is higher for young to middle-aged adults than among youth and senior populations. In 2007, approximately 140,000 Canadians between the ages of 15 and 17 were smokers (approximately 10% of the population in this age group). For those aged 18 years to 24 years, 25 years to 54 years, and 55-plus years, the prevalence was approximately 25%, 22%, and 14% respectively.<sup>5</sup> The prevalence of smokers also varies by provinces. In 2007, the prevalence of smokers in each of ten Canadian provinces was between 14.4% and 24% (Appendix 33). A lower prevalence was observed in British Columbia (14.4%), Ontario (18.2%), and Prince Edward Island (18.4%), and the prevalence of smokers was higher in Quebec (21.7%) and Saskatchewan (24%). However, the rate of smoking decline may be approaching a plateau, and the actual number of smokers has not declined in the last five years.

In 2004 to 2007, the proportion of daily smokers who made at least one quit attempt in the past 12 months was 63% to 69% among teenagers (aged 15 years to 19 years). This rate was higher

compared with young or middle-aged adults and seniors (Appendix 34). Among those older than 45 years, the proportions were 38% to 42%.

A recent study by Leatherdale and Shields<sup>7</sup> showed that the use of pharmacotherapies for smoking cessation was greater in older age groups than in younger age groups. Leatherdale and Shields also reported that the proportion of smokers who used at least one of the pharmacotherapies for smoking cessation was approximately 28% among those aged 15 years to 24 years, 49% among those aged 25 years to 44 years, and 58% among those aged 45 years or older. Overall, nicotine patch was more frequently used compared with other pharmacotherapies. In 2006, approximately 32% of smokers aged 15 years or older reported the use of nicotine patch in the past two years. This was followed by nicotine gum (21%) and other pharmacotherapies (14%). The nicotine patch was more frequently used among those aged 25 years or older. Nicotine gum was more frequently used among those aged between 15 years to 24 years (17.0%) compared with nicotine patch (15.5%) or other pharmacotherapies (2.7%).

In general, the number of claims for nicotine gum continued to increase in the First Nations and Inuit Health Branch (FNIHB) and the Quebec public drug plan during the past five years (Appendix 35). On the other hand, the number of claims for nicotine patch decreased during the same period. However, observed trends do not necessarily reflect actual changes in the total use of NRTs, because it is expected that most NRTs were purchased over the counter. The number of claims for bupropion declined over time in Quebec and FNIHB. The number of varenicline claims in 2007-2008 was greater than that of bupropion, particularly in Quebec (Source: Brogan Inc. Public and Private Drug Plan Databases).

## 6.2 Budget Impact

To assess the budget impact, the authors of this report used insurance claim information from Brogan Inc. that summarized the number of claims and total drug expenditures to the publicly funded drug plans in Canada (Source: Brogan Inc. Public and Private Drug Plan Databases). The perspective of the budget impact analyses was that of publicly funded drug plans. Therefore, expected future expenditures were based on past expenditure patterns that were reported by publicly funded drug plans. Information on claims was available from two publicly funded drug plans: Quebec and FNIHB. The authors of this report used data from Quebec to conduct budget impact analyses because the total number of claims was larger in Quebec than that in FNIHB. Using information from Quebec, we also assessed the budget impact in other jurisdictions, depending on data availability. We considered the budget impact of alternative reimbursement scenarios targeting general populations. This was because, although we also assessed cost-effectiveness targeting specific populations, the assessments of cost-effectiveness were limited to comparisons among a few drugs.

Two scenarios were considered in the analyses. In Scenario 1, we assumed an increase in the number of claims for varenicline, which was found to be an optimal strategy in our cost-effectiveness analyses. In Scenario 2, we assumed an increase in the number of claims for both varenicline and bupropion. The possibility of an increase in bupropion claims was considered because, in the base-case analyses, bupropion and varenicline dominated nicotine gum, patch, inhaler, and lozenge. In addition, the ICER (compared with no intervention) was comparable

between bupropion and varenicline. Therefore, it is reasonable to consider the possibility of an increase in bupropion and varenicline claims.

Budget impact analyses were conducted using the following steps. First, past and future claims and total drug expenditures were calculated. Second, using the Quebec data, the predicted number of claims in other jurisdictions was obtained. Third, the budget impacts in two scenarios were assessed for each jurisdiction.

### 1) Steps to calculate the total number of claims and expenditures:

- *Identify claim data:* The claim data of publicly funded drug plans in Quebec and FNIHB were obtained from Brogan Inc. for fiscal years 2003-2004 to 2007-2008 (Source: Brogan Inc. Public and Private Drug Plan Databases). The number of claims for nicotine patch, nicotine gum, bupropion, and varenicline was available (Appendix 35).
- *Calculate the total number of claims and total expenditures:* Based on the claim data that was identified in step 1, first bullet, the annual total number of claims and total expenditures were calculated for gum, patch, bupropion, and varenicline during fiscal years 2003-2004 to 2007-2008 in each jurisdiction (Appendix 35).
- *Calculate the average cost per claim:* Using Quebec data, the average cost per claim for each drug was calculated by dividing the total drug expenditures over five fiscal years by the total number of claims over the same period (Appendix 36). The total number of claims for varenicline was reported in fiscal year 2007-2008 only. Therefore, the average cost per claim for varenicline was determined by dividing the total expenditures in 2007-2008 by the total number of claims in 2007-2008.
- *Calculate the percentage change in the number of claims:* For gum, patch, and bupropion, the percentage change in the number of claims from the previous fiscal year was obtained in each fiscal year in Quebec. This was done by calculating the rate of change as follows:  $(CL_{t+1} - CL_t)/(CL_t)$ , where  $CL_t$  is the number of claims reported in fiscal year  $t$  and  $CL_{t+1}$  is the number of claims reported in fiscal year  $t+1$ . Then, the average percentage change in claims over the five fiscal years was calculated by taking the average of the percentage change in the number of claims over the five fiscal years (Appendix 36). The percentage change in varenicline claims was not calculated because data were only reported in 2007-2008.
- *Predict the future gum, patch, and bupropion use:* Future changes in the number of claims for gum, patch, and bupropion in Quebec in fiscal years 2008-2009, 2009-2010, and 2010-2011 were estimated by multiplying the reported number of claims in 2007-2008 by the average annual percentage change in the number of claims obtained in step 1, fourth bullet (Appendix 37).
- *Predict the future varenicline and bupropion use:* Future changes in the number of claims for varenicline and bupropion in Quebec were assessed by assuming an annual proportional increase in the number of claims of varenicline by 5%, 10%, 20%, 30%, 40%, and 50% from the previous fiscal year (Appendix 37).
- *Calculate the total predicted expenditures:* The predicted expenditures on gum, patch, bupropion, and varenicline in Quebec were calculated by multiplying the predicted number of claims obtained in step 1, fifth bullet, and step 1, sixth bullet, by the average cost per claim of each drug obtained in step 1, third bullet. The total predicted

expenditure was calculated by adding the total predicted expenditures for each of the four drugs (Table 23).

## 2) Steps to calculate the predicted total number of claims in other jurisdictions:

- *Estimate the total number of claims in 2007-2008:* First, using Quebec data, the average number of claims per smoker for gum, patch, bupropion, and varenicline in 2007-2008 was calculated as follows:

[Average number of claims per smoker]

= [Total number of claims]/[Total number of smokers eligible for reimbursement]

It was assumed that all current smokers in Quebec were eligible for reimbursement (coverage rate = 100%). The total number of claims in 2007-2008 appears in the second columns of Appendix 37. The number of current smokers in Quebec appears in Appendix 33.

Second, the estimated “total number of claims” for other jurisdictions in 2007-2008 was estimated as follows. Based on the above equation, “total number of claims” can be estimated by multiplying the “average number of claims per smoker” by the “total number of smokers eligible for reimbursement.” The average number of claims was based on Quebec data (described previously). The total number of smokers eligible for reimbursement in each jurisdiction was obtained from the Patented Medicine Prices Review Board, which reported the participation rate of the publicly funded drug plans in each jurisdiction in 2003-2004.<sup>277</sup> Information on participation rates was available from four jurisdictions: Alberta, Saskatchewan, Ontario, and New Brunswick. The authors of this report were not able to calculate the number of claims in Alberta using data based on Quebec because Alberta also reimburses for the NRT inhaler, but claim data were unavailable on the NRT inhaler in Quebec (i.e., not reimbursed). Therefore, the estimated number of claims was calculated for the remaining three provinces.

The coverage rate (i.e., the proportion of the total population in a jurisdiction who are eligible for drug benefits) in Saskatchewan, Ontario, and New Brunswick was reported to be 61.3%, 23.3%, and 14.0% respectively. Based on the coverage rate, the total number of smokers eligible for reimbursement in each jurisdiction was calculated by multiplying the coverage rate by the total number of current smokers in the three jurisdictions (shown in Appendix 33). The total number of smokers eligible for reimbursement in Saskatchewan, Ontario, and New Brunswick was estimated to be 116,225, 442,549, and 18,491 respectively.

In calculating the estimated number of claims, we assumed that the use of smoking cessation (both the type and number of attempts) by smokers in the three jurisdictions was comparable to that observed in Quebec. We also assumed that the proportion of smokers who were eligible for reimbursement was the same as that observed in the general population.

The estimated number of claims for gum, patch, bupropion, and varenicline in three jurisdictions in 2007-2008 is shown in the second columns of Appendix 37. Because all

three provinces do not currently cover any of the smoking cessation drugs, the estimated number of claims represents claims made in 2007-2008 if these drugs had been covered in each jurisdiction.

- *Estimate the predicted number of claims from 2008-2009 to 2010-2011:*

The predicted number of claims for gum, patch, and bupropion was calculated by multiplying the reported number of claims in 2007-2008 (obtained in step 2, first bullet) by the average annual percentage change in the number of claims based on the Quebec data (step 1, fourth bullet). Therefore, it was assumed that the average changes in claims in other jurisdictions were the same as those observed in Quebec. The predicted number of claims for bupropion (used in Scenario 2) and varenicline was calculated by multiplying the reported number of claims in 2007-2008 (obtained in step 2, first bullet) by the annual proportional increase in the number of claims of bupropion and varenicline of 5%, 10%, 20%, 30%, 40%, and 50% from the previous fiscal year. The results appear in Appendix 37 (third to fifth columns).

### 3) Steps to assess budget impact

- *Calculate the average cost per claim in Saskatchewan, Ontario, and New Brunswick:* Average costs per claim for NRT, bupropion, and varenicline for these three jurisdictions were based on estimates obtained from the Quebec data (Appendix 36). We assumed the patient copayment in Quebec was 32%.<sup>278</sup> In Saskatchewan, Ontario, and New Brunswick, we considered 0% copayment (i.e., full reimbursement).<sup>259</sup> Therefore, the average cost per claim based on the Quebec data was multiplied by 1.47 ( $=1/[1-0.32]$ ) to reflect the net cost per claim to the three jurisdictions, assuming that the average cost per claim was comparable to that in Quebec. The average costs per claim in the three jurisdictions are reported in the last column of Appendix 37.
- *Calculate total expenditures:* Total expenditures in each jurisdiction during each fiscal year were obtained by multiplying the predicted number of claims by the average cost per claim for each drug and adding the expenditures on each drug (Appendix 37). The results appear in Table 23. In the base-case scenario, the total expenditures to drug plans in jurisdictions other than Quebec were zero because gum, patch, bupropion, and varenicline are not currently reimbursed.
- *Calculate the budget impact analyses:* The budget impact was assessed by subtracting the total expenditures in the base-case scenario from the total expenditures under each scenario.

**Table 23: Budget Impact Analyses**

	Total Estimated Expenditures in 2007-2008	Predicted Expenditures and Budget Impact		
		2008-2009	2009-2010	2010-2011
<b>NEW BRUNSWICK</b>				
<b>Base-case*</b>				
	\$0.00	\$0.00	\$0.00	\$0.00
<b>Scenario 1: % annual increase in claims for varenicline</b>				
5%	--	\$465,721	\$489,007	\$513,457
10%	--	\$487,898	\$536,688	\$590,356
20%	--	\$532,252	\$638,702	\$766,443
30%	--	\$576,606	\$749,588	\$974,465
40%	--	\$620,961	\$869,345	\$1,217,083
50%	--	\$665,315	\$997,973	\$1,496,959
<b>Scenario 2: % annual increase in claims for varenicline and bupropion</b>				
5%	--	\$500,861	\$525,904	\$552,199
10%	--	\$524,712	\$577,183	\$634,901
20%	--	\$572,413	\$686,895	\$824,274
30%	--	\$620,114	\$806,148	\$1,047,992
40%	--	\$667,815	\$934,941	\$1,308,917
50%	--	\$715,516	\$1,073,274	\$1,609,911
<b>ONTARIO</b>				
<b>Base-case*</b>				
	\$0.00	\$0.00	\$0.00	\$0.00
<b>Scenario 1: % annual increase in claims for varenicline</b>				
5%	--	\$6,697,411	\$7,032,282	\$7,383,896
10%	--	\$7,016,336	\$7,717,969	\$8,489,766
20%	--	\$7,654,184	\$9,185,021	\$11,022,025
30%	--	\$8,292,033	\$10,779,643	\$14,013,536
40%	--	\$8,929,882	\$12,501,834	\$17,502,568
50%	--	\$9,567,730	\$14,351,595	\$21,527,393
<b>Scenario 2: % annual increase in claims for varenicline and bupropion</b>				
5%	--	\$7,202,760	\$7,562,898	\$7,941,043
10%	--	\$7,545,748	\$8,300,323	\$9,130,356
20%	--	\$8,231,725	\$9,878,071	\$11,853,685
30%	--	\$8,917,703	\$11,593,013	\$15,070,917
40%	--	\$9,603,680	\$13,445,152	\$18,823,212
50%	--	\$10,289,657	\$15,434,485	\$23,151,728

**Table 23: Budget Impact Analyses**

	Total Estimated Expenditures in 2007-2008	Predicted Expenditures and Budget Impact		
		2008-2009	2009-2010	2010-2011
<b>SASKATCHEWAN</b>				
<b>Base-case*</b>				
	\$0.00	\$0.00	\$0.00	\$0.00
<b>Scenario 1: % annual increase in claims for varenicline</b>				
5%	--	\$668,559	\$701,987	\$737,086
10%	--	\$700,395	\$770,435	\$847,478
20%	--	\$764,068	\$916,881	\$1,100,257
30%	--	\$827,740	\$1,076,062	\$1,398,880
40%	--	\$891,412	\$1,247,977	\$1,747,168
50%	--	\$955,085	\$1,432,627	\$2,148,940
<b>Scenario 2: % annual increase in claims for varenicline and bupropion</b>				
5%	--	\$719,005	\$754,955	\$792,703
10%	--	\$753,243	\$828,567	\$911,424
20%	--	\$821,720	\$986,064	\$1,183,277
30%	--	\$890,196	\$1,157,255	\$1,504,432
40%	--	\$958,673	\$1,342,142	\$1,878,999
50%	--	\$1,027,150	\$1,540,725	\$2,311,087

**Table 23: Budget Impact Analyses (cont'd)**

	Total Estimated Expenditures in 2007-2008	Predicted Expenditures			Budget Impact		
		2008-2009	2009-2010	2010-2011	2008-2009	2009-2010	2010-2011
<b>QUEBEC</b>							
		<b>2008-2009</b>	<b>2009-2010</b>	<b>2010-2011</b>	<b>2008-2009</b>	<b>2009-2010</b>	<b>2010-2011</b>
<b>Base-case<sup>†</sup></b>							
	\$11,011,777	\$9,800,810	\$9,166,567	\$8,635,088	--	--	--
<b>Scenario 1: % annual increase in claims for varenicline</b>							
5%	--	\$9,958,492	\$9,489,815	\$9,132,179	\$157,682	\$323,248	\$497,091
10%	--	\$10,116,173	\$9,828,830	\$9,678,940	\$315,363	\$662,263	\$1,043,852
20%	--	\$10,431,537	\$10,554,166	\$10,930,932	\$630,727	\$1,387,599	\$2,295,844
30%	--	\$10,746,900	\$11,342,574	\$12,409,985	\$946,090	\$2,176,007	\$3,774,897
40%	--	\$11,062,263	\$12,194,054	\$14,135,022	\$1,261,453	\$3,027,487	\$5,499,934
50%	--	\$11,377,626	\$13,108,607	\$16,124,964	\$1,576,816	\$3,942,040	\$7,489,876
<b>Scenario 2: % annual increase in claims for varenicline and bupropion</b>							
5%	--	\$10,001,139	\$9,571,731	\$9,250,529	\$200,329	\$405,164	\$615,441
10%	--	\$10,170,719	\$9,936,327	\$9,838,545	\$369,909	\$769,760	\$1,203,457
20%	--	\$10,509,877	\$10,716,392	\$11,185,005	\$709,067	\$1,549,825	\$2,549,917
30%	--	\$10,849,036	\$11,564,288	\$12,775,660	\$1,048,226	\$2,397,721	\$4,140,572
40%	--	\$11,188,195	\$12,480,017	\$14,630,858	\$1,387,385	\$3,313,450	\$5,995,770
50%	--	\$11,527,354	\$13,463,577	\$16,770,949	\$1,726,544	\$4,297,010	\$8,135,861

\*Reflecting current reimbursement status (i.e., gum, patch, bupropion, and varenicline are not covered).

†Reflecting current reimbursement status (i.e., gum, patch, bupropion, and varenicline are covered).

## 6.2.1 Adopting strategies with optimal cost-effectiveness

### a) **What is the budget impact to the publicly funded drug programs of adopting the strategies that were identified as having optimal cost-effectiveness in the responses to questions 5, 6, 7, and 8?**

In Saskatchewan, Ontario, and New Brunswick, because none of the drugs considered are currently covered, the current and predicted drug expenditures were zero (Table 23). If varenicline is to be covered in these drug plans, the predicted drug expenditures would be positive. In New Brunswick, if varenicline was introduced and if the number of claims of varenicline increased by 5% annually (Scenario 1), then the additional expenditures would be approximately \$466,000, \$489,000, and \$513,000 in 2008-2009, 2009-2010, and 2010-2011 respectively. If the annual increase in the number of varenicline claims was 50%, then the corresponding additional expenditures would be between \$665,000 and \$1.5 million. If the number of claims of varenicline and bupropion increased by 5% to 50% annually (Scenario 2), then the corresponding annual budget impact would be between \$500,000 and \$1.6 million. In Ontario, in Scenario 1, depending on the proportion of annual increase in the number of claims for varenicline, the additional annual expenditures in 2008-2009, 2009-2010, and 2010-2011 would be between \$6.7 million and \$21.5 million. In scenario 2, the annual budget impact would be between \$7.2 million and \$23.2 million. In Saskatchewan, the additional annual expenditures

would be between \$669,000 and \$2.2 million in Scenario 1, and between \$719,000 and \$2.3 million in Scenario 2.

In Quebec, if the current claim pattern follows the historical trend (the base-case scenario), then the total drug expenditures to the drug plan would decline annually from \$11.0 million in 2007-2008 to \$8.6 million 2010-2011 (Table 23). This is because the declining trend of expenditures on patch and bupropion outweighed the additional expenditures resulting from an increasing number of claims for gum and varenicline. Depending on the percentage change in varenicline claims (between 5% and 50%), the annual budget impact in Scenario 1 would be between \$158,000 and \$7.5 million. In Scenario 2, the budget impact would be between \$200,000 and \$8.1 million.

## 6.2.2 Implementing payment or copayment programs

### a) *What is the budget impact to the publicly funded drug programs of implementing a payment or copayment program for the strategies that were identified as having optimal cost-effectiveness in the responses to questions 5, 6, 7, and 8?*

Our economic analyses comparing payment or copayment for pharmacotherapies concluded that payment was more cost-effective compared with no reimbursement. Thus, the budget impact analysis relates to the reimbursing of varenicline and bupropion, which would be the same as that provided in Section 6.2.1.

## 7 ISSUES FOR WILLINGNESS OF SMOKERS TO PAY

What is the evidence of the willingness of smokers to pay for having access to strategies identified as having optimal cost-effectiveness in the responses to questions 5, 6, 7, and 8?

### 7.1 Methods

A protocol was written before the research was started and followed throughout the review.

#### 7.1.1 Literature searches

A peer-reviewed literature search was conducted for the willingness-to-pay for smoking cessation treatments (Question 11). This search strategy was developed by the information specialist with input from the project team.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, BIOSIS Previews, and PsycINFO. The Cochrane Library was searched through the Wiley interface. The Centre for Reviews and Dissemination (CRD) databases were searched through the CRD interface. The PubMed database was searched. A parallel search was run in the Health Economic Evaluations Database (HEED) and in the CINAHL database through the EBSCOhost interface. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were smoking cessation, the specific smoking cessation treatments under review, and the willingness to pay or copay. No

methodological filters were applied to this search. Appendix 1 shows the detailed search strategies.

This search was not restricted by language or publication date. Ovid AutoAlerts were set up to send monthly updates with new literature. Regular updates were performed on HEED, CINAHL, CRD databases, and Cochrane Library databases.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by handsearching the bibliographies of key papers and abstracts of conference proceedings, and through contacts with appropriate experts and agencies.

### **7.1.2 Selection criteria**

Studies from any source, including reviews with information about willingness to pay or copay for optimal treatment strategies, are relevant.

### **7.1.3 Data selection and analysis**

The selection method was described in 4.1.3. The extraction of relevant information was described in 4.1.4. A less stringent data extraction form (Appendix 38) was used. The quality of the selected articles was not assessed because the relevant information could be derived from different types of publication. The relevant information was summarized.

## **7.2 Results**

The flow diagram describing the literature search appears in Appendix 39.

Cost is a barrier to access to smoking cessation medication when a coverage plan does not exist in a jurisdiction. Available data from studies suggest that offering free NRT had an impact in the utilization and efficacy of the medication. It was shown that free nicotine patches increased the enrollment<sup>279-282</sup> and the prevalence of abstinence at six months<sup>280,282,283</sup> and 12 months.<sup>281</sup> Alberg et al. (2004),<sup>279</sup> however, showed that the CARs at six months or more were no longer different between those who received free nicotine patches or no free nicotine patches. Similar results were observed in the study of Hays et al. (1999).<sup>62</sup> A retrospective study<sup>284</sup> analyzing the one-year CARs of participants in a smoking cessation program found that those who received free nicotine gum had a higher success rate than those who purchased the gum individually. West et al., (2005)<sup>285</sup> using sales data to examine the impact of government initiatives to increase access to smoking cessation medicines, found that when bupropion, NRT, and nicotine lozenges were reimbursable, the use of these medications increased.

A population-based survey<sup>286</sup> showed that many smokers would be willing to participate in public health initiatives to reduce the prevalence of smoking through the distribution of free NRT. For insurance coverage, a survey of Californians with insurance<sup>287</sup> found that 62% of respondents indicated that health insurers should offer coverage as part of their standard plans,

and 56% indicated a willingness to pay \$3.00 more for their annual health insurance premium to finance smoking cessation coverage. A full insurance coverage plan had a greater effect on the overall prevalence of smoking than cost-sharing plans.<sup>288</sup> A study using a population-based survey approach of a cohort of women from 15 US states<sup>289</sup> showed that higher levels of coverage for smoking cessation interventions during prenatal care were associated with higher quit rates.

Financial reimbursement for all smoking cessation treatments in The Netherlands has been shown to increase the abstinence rates at six months compared to the control.<sup>195</sup> The difference was maintained after a two-year reimbursement period.<sup>290</sup> Financial incentives for smoking cessation among employees of a multinational company based in the US also indicated a superior success rate as compared with no incentive.<sup>194</sup>

Offering free medications, a public reimbursement plan, and full coverage by health insurance for smoking cessation have a greater impact on the utilization and the success rates. Cost remains a barrier that impedes access to medications. Thus, it affects smoking cessation pharmacotherapy effectiveness. Evidence shows that the general population of smokers may consider using medication as an aid for smoking cessation if the drugs are free or are covered by a publicly funded program or an insurance health plan.

## **8 PLANNING ISSUES FOR OPTIMAL TREATMENT STRATEGIES**

The general relevant planning issues related to equitable access and accountability surrounding the implementation of the treatment strategies that were identified as having, but not limited to, optimal cost-effectiveness were investigated.

### **8.1 Methods**

A protocol was written before the research was started and followed throughout the review.

#### **8.1.1 Literature searches**

A peer-reviewed literature search was conducted for planning issues related to equitable access and accountability surrounding the implementation of smoking cessation treatment strategies (Question 12). This search strategy was developed by the information specialist, with input from the project team.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, BIOSIS Previews, and PsycINFO. The Cochrane Library was searched through the Wiley interface. The CRD databases were searched through the CRD interface. The PubMed database was searched. A parallel search was run in the CINAHL database through the EBSCOhost interface. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were the specific smoking cessation treatments under review, smoking cessation programs, planning/implementing, and

accessibility/equitability/accountability. No methodological filters were applied to this search. Appendix 1 shows the detailed search strategies.

This search was not restricted by language or publication date. Ovid AutoAlerts were set up to send monthly updates with new literature. Regular updates were performed on CRD, CINAHL, and Cochrane Library databases.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by handsearching the bibliographies of key papers and abstracts of conference proceedings, and through contacts with appropriate experts and agencies.

### **8.1.2 Selection criteria**

Studies from any source, including reviews with information about planning issues that are related to equitable access and accountability for optimal treatment, are relevant.

### **8.1.3 Data selection and analysis**

The selection method was described in 4.1. The extraction of relevant information was described in 4.1.4. A less stringent data extraction form (Appendix 38) was used. The quality of the selected articles was not assessed because the relevant information could be derived from different types of publications. The relevant information was summarized.

## **8.2 Results**

The flow diagram describing the literature search appears in Appendix 39.

### **8.2.1 General issues**

Understanding the barriers to the use of smoking cessation services would improve the long-term effectiveness of interventions for diverse types of smokers. Gollust et al. (2008)<sup>291</sup> presented the barriers that all stakeholders including insurance health plans, employers, clinicians, smokers and their families, and the government face. Insurers often perceive that the coverage of cessation interventions is associated with increased costs. Employers are reluctant to ask insurers to include smoking cessation in an employee's benefit plan because of a concern that the benefits of cessation treatments would be lost to competitors when employees change jobs. Clinicians are concerned about reimbursement for nicotine dependence treatment and find that such services are time-consuming. Some physicians lack counselling expertise or are more comfortable with pharmacotherapy than cognitive behavioural counselling. Many smokers are unaware of the available range of smoking cessation alternatives, and most do not believe that cessation services are safe or effective.<sup>292</sup> Gollust et al. (2008) suggested that the government funding of cessation services may be limited because of tight budgets, and policy-makers may be unconvinced that cessation interventions are effective. Gollust et al. (2008) recommended that public policy should include establishing clean indoor air laws, raising cigarette taxes, and expanding coverage for

smoking cessation interventions. Evidence has shown that higher cigarette prices/taxes are associated with a decreased prevalence of smoking and the number of cigarettes smoked. However, the study of Farrelly et al. (2004)<sup>293</sup> showed that smokers tend to switch to stronger cigarettes with higher levels of nicotine and tar in response to higher cigarette prices. Therefore, the health benefits of the increases are nullified by the corresponding increase in tar (a cancer-causing agent) consumption. Farrelly et al. (2004) suggest that higher tar cigarettes be taxed more than lower tar cigarettes.

Issues of accessibility to and selection of drugs may influence the effectiveness of the medications for smoking cessation (NRT, bupropion, and varenicline) in health care. Unlike the results of clinical trials, clinical data from the UK showed that the short-term validated abstinence rates after using NRT were higher than those after using bupropion.<sup>294</sup> Because the level of behavioural support was identical among all participants, the ease to access NRT and the attitude of clients about the safety of bupropion may contribute to the effectiveness of the medications.<sup>294</sup>

## 8.2.2 Issues of specific populations

Specific populations of smokers — including older adults, substance abusers, those with psychiatric disorders, adolescents, those in different ethnic groups, those of low social economic status, and the homeless — often encounter barriers in smoking cessation treatment. Socioeconomic differences including age, gender, education level, marital status, and ethnic disparities help determine the success rates. The identification of barriers and inequalities in disadvantaged populations would increase the success rates of the treatment and quality of life.

Smoking is a risk factor for death in the elderly, who often live with chronic diseases, which can be exacerbated by smoking. Their quality of life can be improved after smoking cessation. Although there are programs that help older adult smokers to stop smoking, the success rates are low. Barriers that contribute to the inaccessibility to smoking cessation among older adults have been identified.<sup>295</sup> First, health care providers often do not advise smoking cessation to elderly patients because of misconceptions about the benefits. They often disbelieve that older adult smokers will stop or assume that older adult smokers are aware of the health risks of smoking. Second, nursing homes may have fewer smoking restrictions than other health care settings. Nursing staff rarely advise residents to quit smoking, and staff who are not smokers are more likely than staff who are smokers to advise cessation. Third, the potential side effects of pharmacological therapy in older adult smokers need to be considered. Because older adults tend to visit physicians often, the authors suggest that routine medical charting include smoking assessment and intervention. As in the general population, a follow-up program could be established for older adult smokers to help in future cessation and prevent relapse.

The high rates of smoking among patients with substance abuse and mental disorders contribute to increased morbidity and mortality. Although smokers with substance abuse and psychiatric disorders seem willing to quit, barriers exist in the provision of cessation interventions.<sup>296,297</sup> The nicotine dependence treatment of patients with substance abuse and mental disorders is often a low priority among policy-makers and providers. Many substance abuse treatment programs are poorly funded, smoking cessation interventions are absent in their mandate, and there is a lack of training for providers.<sup>296</sup> Staff often focus on immediate needs such as housing and safety, and

view smoking cessation as a delayed future task. Health professionals often have insufficient time to advise cessation and thus give this a low priority. Some clinicians believe that cessation will cause an individual's mental health to deteriorate<sup>297</sup> or may cause reoccurrence of a psychiatric disorder, such as depression.<sup>296</sup> Some mental health nurses resist promoting smoking cessation because they view it as a long-term goal and unethical if cessation harms patients' mental health.<sup>297</sup> Recommendations on stop-smoking interventions for patients being treated for substance abuse and mental disorders include higher priority and more flexibility of cessation support, more staff training, and more coordination between primary care physicians and specialists.<sup>297</sup> More research on treatment interventions and health services in these populations is needed.<sup>296</sup>

Smokers of low socioeconomic status face health inequalities and often make unsuccessful attempts to quit smoking. The rates of smoking tend to be higher among people with lower education who are less likely to quit.<sup>298</sup> These people may live stressful lives, have health problems, and use smoking for stress management.<sup>299</sup> The barriers to using existing services include fear of being judged, fear of failure, low awareness about the services, and misconceptions about availability and effectiveness.<sup>300</sup> A group of smokers from a socioeconomically deprived area in the UK<sup>300</sup> expressed a preference for a personalized, non-judgemental approach combining behavioural and pharmacological therapy that is free, convenient, and flexible in timing of service delivery.

Homelessness is another scenario of low socioeconomic status. Homeless smokers face barriers that make cessation difficult. These barriers include the social acceptance of tobacco use among those who are homeless, behaviours such as making their own cigarettes, high level of stress, and smoking in combination with alcohol or illicit drug use.<sup>301</sup> Some health implications could be considered in helping homeless smokers quit smoking, including coverage of pharmacological and behavioural therapy, and incorporation of smoking cessation treatment into addiction recovery programs.<sup>301</sup> Smoking may limit access to assisted housing.

The rates of tobacco use are high in aboriginal communities, where the interventions are less likely to be effective when implemented. Many factors including low socioeconomic status, cultural beliefs, lack of prioritization of tobacco as a health issue, and failure to implement the intervention due to a lack of health care providers stem from the issue of being low priority and a lack of aboriginal involvement in the delivery of health care services.<sup>302</sup> Wardman and Khan (2004)<sup>303</sup> found that 3.8% of First Nations claimants filled a prescription for at least one pharmacotherapy agent. The low rate of cessation pharmacotherapy use in this population could be due to several reasons. Medication use may be inappropriate for First Nations people, and behavioural support may be more appropriate because of their beliefs. Health care providers may lack the skills or time to discuss cessation pharmacotherapy use in a context in which First Nations smokers feel familiar and interested. The relationship between provider and patient may not be established because of a high turnover rate among health care workers in First Nations Communities. First Nations smokers may lack the awareness about the availability of the services. Wardman and Khan (2004) suggest that community members be trained to become service providers. Appropriate cessation strategies need to be developed with the collaboration of community leaders in advocating the use of cessation pharmacotherapy.

The Canadian Task Force on Illicit Tobacco Products (2009) suggest that the aboriginal communities' roles in the production and merchandising of contraband tobacco products leads to large quantities of such products being available in the communities and sustains tobacco consumption.<sup>304</sup> Cheap tobacco products reduce the perceived cost benefits of cessation and serve as a disincentive to cessation attempts.<sup>305</sup> The increasing availability of contraband tobacco “sabotages” the likelihood of cessation, particularly in low socioeconomic groups, because it lowers the cost of smoking and removes the economic “advantage” of cessation products. Luk et al. (2009) suggest there is a need for increasing security at the borders to make it more difficult to obtain contraband cigarettes.

Most smokers start smoking during adolescence, which is the time for the transition from experimentation to dependence. Challenges remain in the development of effective interventions for young smokers. Henningfield et al. (2000)<sup>306</sup> presented issues that required study, including the applicability of adult-validated treatments in a young population; a consideration of adolescent nicotine dependence and potential pharmacologic adjuncts; a consideration of social, health, risk perception, and interpersonal factors that may facilitate or inhibit cessation attempts among youths; and advanced cessation trials research designs and measurement. Younger smokers, including adolescents, tend to use fewer cessation aids.<sup>7</sup> An interview conducted with a group of youth smokers found that their preferences for smoking cessation were to receive support from friends and family, to be able to access NRT, and to participate in a flexible non-school-based cessation program.<sup>307</sup> Strategies for the prevention of smoking in youth include age restrictions in the legal purchase of tobacco, restricted tobacco promotion targeting minors, increased price of tobacco products, and parental tobacco control.<sup>308</sup> Child health care clinicians also play a role by including diagnosis and treatment of youth tobacco dependence in their practice.<sup>308</sup>

### **8.2.3 Accountability**

The followings are suggestions that were collected during literature review.

Government agencies, health care programs, services, and practitioners could be held accountable for quality, safety, and cost-effectiveness in smoking cessation treatment.<sup>309,310</sup> Tobacco dependence is viewed as a chronic relapsing addictive disorder requiring treatment that is applied using the same standards as those for other chronic diseases and mental conditions.<sup>311</sup> Government agencies and health care providers could have proactive plans to provide the public with scientifically sound information about the risk of tobacco product use, so that the public can make informed decisions.<sup>311</sup> The tobacco industry could be accountable for its actions and the adverse consequences of using its products. Those who attack tobacco cessation programs could be held accountable for their actions.<sup>312</sup>

Curry et al. (2008) and Davis et al. (2000) suggest there is a need for a national training and accreditation program so that the treatment of tobacco use and dependence is accountable and standardized across all jurisdictions. Program services need to establish a performance framework with organizational and managerial accountability.<sup>313</sup> The key elements could include the systematic identification of priority groups, the allocation of sufficient time and resources for a national standard training of staff, and long-term funding to achieve the objectives. Targeting and reaching disadvantaged groups could be set as a priority, and guidance on how to reach these

groups could be given.<sup>314</sup> Health authorities could employ dedicated staff to develop a specialist smoking treatment service. A detail monitoring system could be developed and all services could meet a minimum standard in order to qualify for funding.<sup>315</sup> Clinical information systems and electronic health records could be designed to permit standardized reporting.<sup>310</sup> Pharmacotherapy could be used in conjunction with psychosocial and physiological treatment.<sup>316</sup> Success rates could be monitored on a long-term basis and could be conducted through a central research body.<sup>314</sup> A quality control system for smoking cessation services needs to be in place to assure the delivery of high-quality treatment. Most Canadian hospitals have no means of identifying admitted patients who are smokers, and do not provide systematic assistance with cessation to such patients — this despite evidence that more than 30% of Canadian hospital beds are occupied by adults who are there solely as a consequence of their smoking.<sup>317</sup>

Addressing tobacco use could be a standard of care and expected competency for all clinicians (clinician's accountability). The results of a survey<sup>318</sup> asking Ontarians about their views about health professionals who provide advice for smoking cessation showed that approximately two-thirds of respondents viewed physicians as a good source of advice on quitting. More than half of current smokers would be likely to ask a physician for quit advice. Given that clinicians can advise smokers to quit, they might be held legally accountable for not providing cessation services in accordance with guidelines.<sup>291</sup> Tobacco interventions need to become a standard of nursing practice,<sup>319</sup> which would require changes in nursing curricula, education to ensure clinical competency, research to determine best educational strategies, and practice accountability including licensure, certification, and performance measures. Clinicians and staff members could make a commitment to systematically help patients quit smoking by performing the five "A's" (ask, advise, assess, assist, arrange).<sup>309</sup> Many experts are talking about an "ABC" model: Always ask and reflect Best practice in always offering Cessation assistance. In return, patients could expect that tobacco use will be addressed as part of their routine health care (patients' accountability).

## **9 PUBLICLY FUNDED PROGRAMS IN CANADA**

The current public reimbursement status of pharmacologic agents for smoking cessation was investigated.

### **9.1 Methods**

Information was obtained from the websites of jurisdictions.

### **9.2 Results**

The publically funded programs in Canada that reimburse for the use of pharmacologic agents as an aid for smoking cessation appear in Table 24. Alberta, Quebec, and the First Nations and Inuit Health Branch have limited coverage for nicotine gum, nicotine patch, and bupropion. Varenicline is covered as limited use in Quebec, Yukon, and the First Nations and Inuit Health Branch. The coverage of varenicline is under review in Alberta.

**Table 24: Public Reimbursement Status of Pharmacological Agents for Smoking Cessation\* (Canadian drug plan coverage as of June 2009)**

Drug Plan	Coverage
Alberta	Nicotine gum, patch, and inhaler are covered as limited use (lifetime maximum of \$500 per participant; not eligible for coverage for Alberta Seniors and Community Supports participants). Bupropion (Zyban) (150 mg sustained release) covered as regular benefit status. Coverage of varenicline being reviewed. <sup>261</sup>
Quebec	Nicotine gum, patch, Zyban, and varenicline (Champix) covered as limited use (limited to 12 consecutive weeks per 12-month period; reimbursement of chewing gum limited to 840 pieces for those 12 weeks). <sup>320</sup>
Yukon	Nicotine gum, patch, and inhaler not listed. Zyban (150 mg sustained release) under regular coverage for Children’s Drug and Optical Plan and Pharmacare and Extended Benefits. Champix has exception drug status for Pharmacare and Extended Benefits (for adults who have failed to quit smoking and want pharmacologic help; limited to 12-week course [165 tablets] in 12-month period and combined with intensive counselling; coverage must be applied for). <sup>321</sup>
Non-Insured Health Benefits (NIHB) Program for First Nations and the Inuit	Nicotine gum and patch, Zyban and Champix covered as limited use. During 12-month period, nicotine gum limited to 945 pieces. Nicotine patch limited to 84 patches for Habitrol and 70 patches for Nicoderm and Nicotrol. Zyban (150 mg sustained release) limited to 180 tablets during 12-month period. Champix limited to 165 tablets during a 1-year period. <sup>322</sup>
Veterans Affairs Canada	Nicotine patch, Zyban, and Champix not standard benefits. Special authorization needed. To access benefits, clients need prescription and to be able to show a medical need that is most appropriately met with requested therapy. <sup>323</sup>
Other jurisdictions	Nicotine gum and patch, Zyban, and Champix not covered by drug plans in British Columbia, Newfoundland and Labrador, Manitoba, New Brunswick, Northwest Territories, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan.

\*This table lists coverage for bupropion (as Zyban) specifically for smoking cessation. Bupropion coverage for depression is not listed.

## 10 DISCUSSION

### 10.1 Summary of Results

#### 10.1.1 Clinical

- Most of the included studies were scored using the Hailey scale as being of high quality: 53% were rated A, 21% were rated B, 19% were rated C, 6% were rated D, and 1% was rated E.
- In the general population, nicotine replacement therapies (patch, gum, lozenge, inhaler, spray, and sublingual), bupropion, and varenicline were all efficacious as an aid in smoking cessation compared with placebo. Varenicline was found to be superior to conventional NRT use and bupropion. There were no differences in efficacy between bupropion and NRT or

between the various forms of NRT alternatives (patch, gum, lozenge, nasal spray, sublingual). All pharmacotherapy-treated groups had higher relapse rates than the placebo groups.

- The common adverse events associated with each pharmacotherapy that were found to occur at an increased frequency compared with placebo were:
  - Bupropion: headache, dizziness, nausea or vomiting, constipation or diarrhea, sleep disturbance, insomnia, and dry mouth.
  - Varenicline: headache, dizziness, nausea or vomiting, gastrointestinal disturbance, constipation or diarrhea, sleep disturbance, insomnia, and abnormal dreams.
  - Nicotine patch: headache, sleep disturbance, abnormal dreams, and skin reactions.
  - Nicotine gum: gastrointestinal disturbance, and hiccups.
  - Nicotine lozenge: nausea or vomiting, gastrointestinal disturbance, and hiccups.
  - Nicotine inhaler: gastrointestinal disturbance, sore or irritation throat, hiccups, and coughing.
  - Nicotine spray: nausea or vomiting, sore or irritation throat, coughing, runny nose, sneezing, and watery eye.
  - Nicotine sublingual: nausea or vomiting, and gastrointestinal disturbance.
- Among the combined pharmacotherapies that were tested in the general population, nicotine patch plus nicotine spray was found to be more efficacious than nicotine patch. The addition of nicotine gum to nicotine patch was superior compared with nicotine patch in the six-month continuous abstinence rate, but not at one year follow-up. There were no differences between other groups such as nicotine inhaler plus nicotine patch versus nicotine inhaler, bupropion plus nicotine gum versus bupropion, bupropion plus nicotine patch versus bupropion, and nicotine patch plus bupropion versus nicotine patch.
- Adding behavioural support to nicotine patch, nicotine gum, or bupropion did not increase the efficacy of the drugs. The addition of nicotine patch or nicotine gum to behavioural support produced a trend of increased abstinence rates compared with behavioural support.
- Evidence about the impact of payment on the clinical effectiveness of drugs that are used for smoking cessation therapy was limited. Financial reimbursement and incentives seem to be more efficacious in smoking cessation. However, providing free nicotine patches did not improve smoking cessation compared with the over-the-counter approach.
- Each specific population was treated differently, and most outcome measures could not be pooled because of heterogeneity in populations and interventions.
  - *Adolescent*: Nicotine patch seemed to be efficacious in smoking cessation compared with placebo. The effect of nicotine gum was uncertain. Adding bupropion to nicotine patch did not improve smoking cessation.
  - *Substance abuse*: Nicotine patch was more effective than placebo at six-month follow-up. The addition of nicotine gum to nicotine patch produced no difference compared with nicotine patch plus placebo gum until 12-month follow-up. The addition behavioural support to NRT did not improve the overall abstinence rates.
  - *Mental disorder*: Nicotine patch plus behavioural support did not improve smoking cessation compared with usual care. There was no difference between placebo and bupropion. The addition of bupropion to nicotine patch did not increase cessation rates.
  - *Depression*: The efficacy of nicotine gum versus placebo was unclear because of mixed results. There were no differences between bupropion, nicotine patch, and placebo.
  - *Posttraumatic stress disorder*: Evidence was limited (one small trial) and inconclusive.

- *Pregnant women:* There was no difference in smoking abstinence between nicotine patch and placebo, nicotine gum and placebo, or NRT plus behavioural support, and behavioural support.
- *Cardiovascular or smoking-related diseases:* Nicotine gum, nicotine patch, bupropion, and varenicline were efficacious as an aid for stopping smoking compared with placebo. Adding behavioural support to nicotine patch did not increase the overall abstinence rates of nicotine patch. Nicotine patch plus nicotine inhaler plus bupropion was more effective than nicotine patch.
- *COPD:* Nicotine sublingual was more efficacious than placebo. Bupropion was better than placebo.
- *Hospitalized patients:* The difference in abstinence rates between nicotine patch and placebo or between bupropion and placebo was not found. Nicotine patch plus behavioural support did not improve smoking cessation compared with nicotine patch or behavioural support. Compared with usual care, NRT plus behavioural support yielded mixed results that were due to clinical and intervention heterogeneity.
- *Low-income:* Nicotine patch plus behavioural support showed no difference in smoking abstinence compared with nicotine patch or behaviour support.
- *Cancer:* Limited evidence showed no difference in smoking abstinence between usual care and nicotine patch plus behavioural support.

### 10.1.2 Planning Issues

- Cost is a barrier to access to smoking cessation medication when coverage plans do not exist in a jurisdiction. Evidence showed that the provision of free drugs, a reimbursement program, and full insurance coverage increased enrollment and had an impact on use and success rates.
- Stakeholders including smokers, clinicians, government, employers, and health insurance providers face barriers that affect the long-term effectiveness of cessation interventions among diverse types of smokers.
- There are barriers and health inequalities in specific populations. Among older adults, the issues include inaccessibility to smoking cessation, misconceptions of health care providers, and potential side effects of pharmacotherapy. Smoking cessation therapy in mental disorder patients has been a low priority, and some health care professionals are reluctant to recommend smoking cessation treatment, believing that stopping smoking could harm patients' mental health. Smokers of low socioeconomic status have encountered barriers in using existing services including fear of being judged, fear of failure, low awareness about existing services, and misconceptions about availability and effectiveness. Homeless smokers faced barriers including social acceptance of tobacco use, high level of stress, and smoking in combination with substance abuse. Factors that contribute to the low success rate among aboriginal people include low socioeconomic status, distinct cultural beliefs, lack of prioritization of tobacco as a health issue, and lack of aboriginal involvement in delivery of health care services. Effective intervention for younger smokers required more research and development because adult-validated treatments may not apply to a young population.
- Government agencies, health care programs, services, and practitioners could be held accountable for quality, safety, and cost-effectiveness in smoking cessation treatment. There is a need for a national certification program, where the treatment of tobacco use and dependence would be accountable and standardized across all jurisdictions. Program services need to establish a performance framework with clear organizational and managerial

accountability. Patients could expect that tobacco use will be addressed as part of their routine health care.

- Alberta, Quebec, and the First Nations and Inuit Health have limited coverage for nicotine gum, nicotine patch, and bupropion. Varenicline is covered as limited use in Quebec, Yukon, and the First Nations and Inuit Health.

### 10.1.3 Economic

- A review of existing economic analyses showed that varenicline (with or without behavioural interventions) seemed to be the most cost-effective therapy, followed by bupropion and NRT. However, the results should be interpreted with caution because most of the studies comparing varenicline with bupropion or NRT<sup>206,211,217,219,220</sup> were funded by the manufacturer of varenicline.
- Our economic analyses targeting a general population showed that, for all ages and gender, bupropion and varenicline dominated (i.e., cost less and more effective) nicotine gum, patch, lozenge, and inhaler. If providers' willingness to pay was greater than \$10,000 per QALY, then varenicline was preferred.
- Adding 10- to 15-minute telephone counselling to nicotine patch therapy may not be cost-effective compared with the patch alone therapy.
- Analysis of reimbursement was limited to consideration of bupropion and NRT. Analysis found that providing full reimbursement of smoking cessation therapy was cost effective compared to no reimbursement as long as a decision maker was willing to spend at least \$1,026 per QALY gained.
- Analysis of the cost effectiveness of cessation interventions for cardiovascular patients was restricted to bupropion and NRT (gum, patch, inhaler, or patch plus inhaler). As long as a decision maker was willing to spend at least \$3,759 per QALY gained, bupropion was the optimal treatment choice.
- Analysis of the cost effectiveness of cessation interventions for hospitalized patients was restricted to bupropion and NRT patch. If a decision maker was willing to spend at least \$10,143 per QALY gained, bupropion was the optimal treatment choice. However, if a decision maker was willing to spend more than \$86,406 per QALY gained, NRT patch may be cost effective.
- Potential budget impact was predicted for the time periods, 2008-2009, 2009-2010 and 2010-2011. Impact was evaluated by assuming a proportional increase in the number of claims of varenicline and bupropion (ranging from 5% to 50%) in four jurisdictions: New Brunswick, Ontario, Quebec, and Saskatchewan. In New Brunswick, if varenicline is to be reimbursed, the annual additional expenditure would be between \$466,000 and \$1.5 million, depending on the percentage increase in varenicline claims. In Ontario, the annual budget impact would be between \$6.7 million and \$21.5 million; in Saskatchewan, it would be between \$669,000 and \$2.2 million. In Quebec, if the number of varenicline claims increased, the budget impact would be between \$158,000 and \$7.5 million. If both varenicline and bupropion were to be reimbursed, the corresponding budget impact would be between \$500,000 and \$1.6 million in New Brunswick, between \$7.2 million and \$23.2 million in Ontario, and between \$719,000 and \$2.3 million in Saskatchewan. If the varenicline and bupropion use increased, the budget impact would be between \$200,000 and \$8.1 million in Quebec. It is worth noting

that varenicline prescriptions grew by 350% in 2008, beyond the assumed range of 5% to 50% increase in varenicline claims each year.<sup>324</sup>

#### 10.1.4 Comparison with relevant recent literature

While this CADTH report was in its last stages of development, the Medical Advisory Secretariat of the Ontario Ministry of Health and Long-Term Care released a review entitled *Population-Based Smoking Cessation Strategies*<sup>325</sup> in its Ontario Health Technology Assessment Series. The report was a summary of reviews, mainly Cochrane reviews, for clinical evaluations and economic studies for economic evaluations, focusing on cessation strategies in Ontario. A systematic review or economic analysis was not performed.

For the clinical assessment, the Ontario report reviewed the efficacy of nine population-based smoking cessation strategies (non-pharmacological and pharmacological interventions). The populations in pharmacotherapy studies were limited to healthy individuals. Direct comparison was used for data analyses (drugs were compared to placebo or to other pharmacotherapy). The primary outcome was abstinence from smoking after at least six months of follow-up. However, continuous abstinence and point prevalence abstinence were not analyzed separately. This CADTH report is a systematic review and meta-analysis focusing on the assessment of the clinical efficacy of varenicline (nicotine receptor partial agonist), bupropion (antidepressant), and NRT (six forms of nicotine replacement therapy) among all smokers. The effect of adding behavioural support and the impact of payment or no payment on the efficacy of pharmacotherapy was evaluated in this report. Mixed treatment comparisons meta-analysis was used to perform direct and indirect comparisons between drug classes and among six forms of NRT. Our primary outcome was abstinence from smoking for at least six months of follow-up with biochemical verification. The continuous and point-prevalence abstinence at different time points were analyzed separately in our report. Both reports found that varenicline, bupropion, and NRT were better than placebo; and varenicline was superior to NRT and bupropion.

For the economic assessment, the Ontario report reviewed a recently published systematic review of economic studies<sup>326</sup> to provide a summary of the cost-effectiveness evidence on non-pharmacological and pharmacological smoking cessation interventions. The Kahende et al.<sup>326</sup> study was based on 42 economic studies assessing the cost-effectiveness of cessation interventions including mass media campaigns of various forms (e.g., television, posters), community-based interventions (e.g., pharmacist-directed program), and counselling (e.g., by telephone, physicians, nurses). The Ontario report concluded that most interventions reviewed were cost-effective. However, the report also concluded that the cost-effectiveness results needed to be interpreted with caution due to limited data on clinical effectiveness. In general, the ICERs summarized in the Ontario report on pharmacological interventions were lower than those obtained in our economic modelling study (after currency conversion and adjusting for inflation). The differences in the models used and in the input parameters and model assumptions between studies might result in different ICERs. Moreover, the systematic review by Kahende et al.<sup>326</sup> did not include recent cost-effectiveness studies of varenicline.

In addition to the assessment of clinical effectiveness and the performance of an economic review and analysis, a budget impact, reviews of the issues of equitable access and

accountability, and the current public reimbursement status of pharmacological therapies among Canadian jurisdictions were also included in CADTH's report.

Some differences compared to US guidelines<sup>327</sup> are also noteworthy. The abstinence rates in this report were analyzed separately based on type of medication used, type of abstinence, follow-up period, and patient populations. Medications and patient populations were not collapsed to compare the effects of medication alone versus medication plus different types of behavioural interventions, as conducted in the review of the US guidelines. Thus, compared to the US guidelines, the current report with its strict selection criteria, together with a different approach to analysis, may not exactly reveal the benefit of adding behavioural support to drug therapy.

## 10.2 Strengths and Weaknesses of This Assessment

### 10.2.1 Clinical

This report is a systematic review of the efficacy of three drug classes that are used as pharmacotherapy for smoking cessation in general and specific populations of smokers. The authors of this report systematically reviewed 155 reports describing 143 RCTs. A Bayesian random-effects modelling technique of mixed treatment comparisons was used. The long-term effects NRT including patch, gum, lozenge, spray, inhaler, and sublingual were analyzed separately and compared among themselves and with bupropion and varenicline. The collected cessation rates were classified according to definition (i.e., continuous abstinence, prolonged abstinence, and weekly point prevalence abstinence) and analyzed separately. All potential adverse events that were associated with pharmacotherapies were analyzed. Studies on the efficacy of combined pharmacotherapy compared with monotherapy were included. The impact of adding behavioural support and the impact of pay versus no pay on the effectiveness of drug therapy were investigated. The inclusion of studies with a follow-up of at least six months eliminated short-term effects, where the abstinence rates were usually non-sustainable. In fact, abstinence rates were inversely related to time of follow-up. The outcome of cessation was limited to biochemical validation of the abstinence rate to minimize false data on quit attempts.

One limitation of the evidence was the variation in abstinence rates between studies. Differences in dosage, gender, age, and degree of nicotine dependence might account for the variations. Depending on the degree of nicotine dependence of smokers, the study design usually involved titration of the dosage. This review did not analyze the effect of pharmacotherapy on heavy smokers, because the standard dose of drugs might be less effective in this population. The analysis in our review did not account for drug dosage, which may be a source of bias in outcome comparison. The effect of gender on the clinical effectiveness of pharmacotherapies was not considered in this review. Evidence has shown that there is a difference in the benefits of NRT for men and women.<sup>328,329</sup> There was also evidence that disputed the differential effect of NRT based on gender.<sup>330</sup> Most studies included an adult population of greater than 18 years of age, but did not stratify the effectiveness based on age group. MTC meta-regression was not done to address the heterogeneity of study characteristics. However, the effects of pharmacotherapies on specific populations were analyzed separately.

Another limitation of the evidence was the variation in outcome measurements and timing of measurement, which made the analyses more complex and difficult to interpret. Three types of

abstinence rates including continuous abstinence, prolonged abstinence, and seven-day point prevalence abstinence, with different follow-ups (six months and one year), contributed to six possible combinations. Some studies showed a between-groups difference for one type of abstinence, but not others. This made cross comparisons difficult. Attention could be given to differentiate which type of abstinence was used in the analysis of the efficacy. The continuous abstinence rate was often lower than the point prevalence abstinence. Also, many studies had small sample sizes. The longer the duration of follow-up, the lower the abstinence rates were. The long-term efficacy of the drug was therefore often lost with small sample sizes or when it was based on the continuous abstinence rate.

The types of behavioural supports that were used as adjuncts to pharmacotherapies varied between trials. This contributed to the bias in the comparison of outcomes. No attempt was made in this review to study the effects of differences in behavioural supports, because this was beyond the scope of this report. Within the limits of our selection criteria, evidence from the identified trials did not show any strong impact of adding behavioural support to pharmacotherapy in overall abstinence rates. The results from most trials surrounding the inclusion of behavioural support were summarized using a qualitative approach because of the diversity in behavioural interventions. The only exception was for cases in the relatively healthy smokers. The potential reasons for differences compared with other work such as the US guidelines were addressed in section 10.1.3.

Although the analyses of specific patient populations were performed separately, there still existed heterogeneity within each population group, as well as in the interventions and comparators within and between populations. Obtaining the effect sizes was sometimes not possible, and the results were descriptively reported based on the findings of individual trials. It was difficult to determine whether a drug, for instance nicotine patch, was efficacious across specific populations because of a lack of evidence.

### **10.2.2 Economic**

The authors of this report conducted a systematic review of economic studies on the cost-effectiveness of pharmacological interventions for smoking cessation and the cost-effectiveness of paying or copaying for such interventions. Our review identified limited evidence to answer our research questions, leading us to conduct a full economic evaluation tailored to a publicly funded drug plan in Canadian jurisdictions. Therefore, study implications are, in general, useful to each jurisdiction for a resource allocation decision. Our economic models are comprehensive because we addressed heterogeneity in cost-effectiveness by assessing age-, gender-, and disease-specific populations. The decision analytic models in this report are also complex, reflecting the complex impacts of smoking on multiple and interrelated chronic conditions. Efforts were made to simplify the models without compromising their comprehensiveness — a major challenge of building models for preventive interventions that potentially impact a wide variety of chronic conditions. Moreover, we not only provided cost-effectiveness results based on currently available information, but also quantified the expected cost of a decision based on current (but imperfect) information using EVPI analyses. Through EVPPI analyses, we also identified future research priorities in the assessment of cost-effectiveness of smoking cessation interventions. In particular, we were able to identify types of parameters and population subgroups that need to be prioritized in future research for reducing decision uncertainty. The

results from the value of information analyses are useful to decision-makers in acknowledging the level of uncertainty in decision-making based on currently available information.

Some study considerations are noteworthy in interpreting our results. First, our model over-predicted mortality compared with the observed data for those aged 30 years and older. The over-prediction will likely indicate that the interventions are more cost-effective than they actually are. Nonetheless, because the differences in discounted LYs were less than one year after the calibration, the potential impacts of the model over-prediction on study implications are likely to be minimal.

Second, it has been shown that different preference-based measures do not provide the same utility scores for the same health states.<sup>331,332</sup> Such differences arose partly from the differences in methodological and theoretical constructs among instruments. Therefore, although any preference-based measures are on the common scale of 0 (dead) to 1 (perfect health), it is not ideal to consider them to be interchangeable when used in cost-effectiveness analyses.<sup>331-333</sup> In our economic models, efforts were made to base utility scores for all health states on a single preference-based instrument. However, because of a lack of data and existing studies, the utilities for health states used in our models were based on two instruments: EQ-5D and HUI3. It has been often observed that health state valuations based on EQ-5D and HUI3 for the same health state differed even though they were derived from the same respondents.<sup>332,333</sup> This was partly due to differences in the way that health-related quality of life was conceptualized and operationalized, and in the way that scoring functions were derived between the two instruments. Therefore, the utility scores for health states that were based on EQ-5D could be different had HUI3 been used consistently throughout our models (and vice versa).

Third, the face validity of estimated utility scores for smokers and quitters may be noteworthy. For example, when we estimated utilities for smokers and quitters using the CCHS data, the utilities of smokers were often quantitatively and importantly higher (i.e., difference in overall HUI3 score of 0.03 or greater<sup>3</sup>) than those of former smokers. This may be partly due to healthy survivor effects (i.e., smokers who responded to the survey were those who were healthy enough to survive). Therefore, the utilities of smokers may be greater than those of quitters because of selection. On the other hand, the utilities of quitters may be lower than those of smokers because former smokers stopped smoking because of deteriorating health (the issue of temporality). Our finding implies that it may be important to explore this longitudinally to understand the changes in utility scores since cessation. Despite several potential sources of uncertainty in utility measurements, the authors of this report found that EVPPI of utility scores were negligible in all economic models, indicating that uncertainties around utility scores contributed little to overall decision uncertainty.

Fourth, there has been ongoing debate about whether economic models should include the costs resulting from added LYs from interventions. In the context of smoking cessation interventions, our model considered two types of costs: intervention costs and health care costs of treating diseases attributable to smoking. The issue is whether future health care costs that are incurred from diseases unrelated to smoking should be included when the costs of added LYs are considered.<sup>334</sup> It has been noted that the total lifetime health care costs of smokers could be lower than those of former smokers<sup>204</sup> because smokers are expected to have shorter life expectancies

than quitters, and smokers are likely to die before developing other diseases not attributable to smoking. Smoking cessation may result in higher total lifetime health care costs. Namely, prolonged LYs through smoking cessation interventions could result in additional future health care costs incurred from diseases unrelated to smoking. In this respect, one view is to include the future health care costs of treating diseases unrelated to smoking in economic analyses. Another view is not to include such costs. One reason for not including unrelated costs is that an inclusion of such costs would result in favour of providing interventions to the elderly instead of young people because young people have a longer life expectancy than the elderly (regardless of smoking status), making it expensive to save the lives of young people.<sup>213</sup> Another reason is that, although the potential costs of treating diseases unrelated to smoking during added LYs could be substantial, these costs will likely occur in the future. Because such future costs will be heavily discounted, the impacts of such costs on cost-effectiveness would be minimal.<sup>206</sup> In this report, we agreed with the latter view and did not include the future costs of diseases unrelated to smoking, acknowledging that the potential impact of including unrelated future health care costs on our results is likely to be minimal.

Fifth, one of the model assumptions was that adherence to pharmacotherapies was not considered in the decision analytic models. An omission of potential differential adherence levels for pharmacotherapies may bias the cost-effectiveness results. However, the study conclusions will change only if there are major differences in adherence levels among pharmacotherapies; such evidence was not reviewed in the clinical analyses, and observational studies are unlikely to be available.

Finally, our budget impact analyses were based on claim patterns observed in Quebec. When calculating the budget impact in jurisdictions other than Quebec, we assumed that the claim patterns in other jurisdictions were comparable to those observed in Quebec. It is likely that the claim patterns in other jurisdictions are not necessarily comparable to those observed from Quebec because the drug coverage policy in Quebec often differs from that in other jurisdictions in the subpopulations covered and the level of coverage. Nonetheless, with a lack of available claim data on publicly funded drug plans, our results would be the best possible predictions of future claim patterns. In addition, when forecasting the number of claims and expenditures, we did not consider the potential impact of a changing prevalence of smoking on the insurance claims for smoking cessation drugs. Therefore, the predicted total expenditures were only based on the prevalence of smoking observed in the past years. Because our budget impact analyses were based on historical claim patterns, the estimates do not necessarily reflect actual changes in claim patterns.

## **10.3 Generalizability of Findings**

### **10.3.1 Clinical**

There was ample evidence on the long-term effect of NRT, bupropion, and varenicline in the general population of smokers who were relatively healthy and motivated to quit. The analyses of the efficacy of these drug classes were based on 10 trials of varenicline versus placebo (N = 2,529), three trials of varenicline versus bupropion versus placebo (N = 2,690), one trial of varenicline versus nicotine patch (N = 757), 19 trials of nicotine patch versus placebo (N = 11,773), 19 trials of nicotine gum versus placebo (N = 9,002), one trial of nicotine lozenge

versus placebo (N = 1,818), two trials of nicotine sublingual versus placebo (N = 488), five trials of nicotine inhaler versus placebo (N = 1,585), four trials of nicotine spray versus placebo (N = 937), two trials of patch versus spray (N = 1,683), one trial of lozenge versus gum (N = 408), one trial of patch versus inhaler (N = 446), 13 trials of bupropion versus placebo (N = 6,101), and one trial of bupropion versus nicotine patch (N = 100). The findings of this review agreed with those of previous meta-analytic reviews<sup>335-340</sup> that reported that varenicline, bupropion, and five nicotine replacement therapies are all superior to placebo at promoting long-term cessation. Our findings also agreed with those of Cahill et al. (2008)<sup>336</sup> who showed that more participants quit successfully more often with varenicline than placebo, and the benefit of varenicline is modest compared to nicotine patch. In addition, the use of mixed treatment comparisons in our review revealed no differences in efficacies when comparing between different NRT, between bupropion and NRT, or between varenicline and NRT, except between varenicline, nicotine patch, and nicotine gum. Thus, NRT, bupropion, and varenicline could all be used as aids for smoking cessation in the general population of smokers. However, the adverse effects that are associated with each treatment need to be monitored. The US Food and Drug Administration issued a warning that psychiatric problems, including suicide, are associated with the use of varenicline and bupropion.<sup>26</sup>

In the general population of smokers, three trials compared nicotine patch to nicotine patch plus behavioural support (N = 818), five trials compared nicotine gum to nicotine gum plus behavioural support (N = 1,205), and one trial compared bupropion to bupropion plus behavioural support (N = 229). No RCT addressed the effect of adding behavioural support to other NRT or to varenicline. Our findings indicated that adding behavioural support to nicotine patch, nicotine gum, or bupropion did not increase the efficacy of the drug. When nicotine patch (one trial, N = 64) or gum (eight trials, N = 2,056) was added to behavioural therapy, there were also no significant differences between groups in abstinence rates. Our findings could not be generalized to the routine use of the treatment because the heterogeneity of the behavioural supports among studies was substantial.

Findings presented in this technology assessment regarding the addition of behavioural therapy to pharmacotherapy warrant clarification. As noted earlier in this report, different forms of behavioural therapy exist, and their relative levels of effectiveness are variable, based on findings from past systematic reviews that explored their impact on quit rates.<sup>341-344</sup> The types of behavioural therapies encountered in our included studies were diverse, consisting of different combinations of brief advice, partner support, relapse prevention, education session, cognitive behaviour therapy, or telephone support. The behavioural treatments were given either on an individual basis or as group counselling provided by nurse practitioners, social workers, psychologists, psychiatrists or physicians.

Our analyses sought to determine whether the addition of any form of behavioural therapy in addition to pharmacotherapy improved quit rates, and therefore a distinction between different forms of behavioural therapy was not made in our analyses. While on average behavioural therapy did not conclusively demonstrate an increased benefit over pharmacotherapy alone in our analyses, this may be a consequence of the decision to group therapies in our comparisons. It is possible that less effective forms of behavioural therapy may have masked the effectiveness of those associated with greater effects, thereby producing a pooled estimate that was suggestive of

clinical benefit but which failed to achieve a conventional level of statistical significance. Thus, it remains possible that specific forms of behavioural therapy may be associated with additional benefit for patients already using pharmacotherapy to aid in their attempt to quit smoking.

There were few RCTs of combined therapy versus monotherapy. Blondal et al. (1999)<sup>183</sup> (N = 239) showed that nicotine spray plus nicotine patch was better than nicotine patch. Similar results were in favour of nicotine patch plus nicotine gum over nicotine patch in the study of Kornitzer et al. (1995)<sup>185</sup> (N = 374). A meta-analytic review by Shah et al. (2008)<sup>345</sup> concluded that combination therapy of NRT is better than monotherapy in smoking cessation treatment. However, the results of the study of Bohadana et al. (2000)<sup>184</sup> (N = 400) did not agree with that conclusion when comparing nicotine inhaler plus nicotine patch to nicotine inhaler. When bupropion was added to nicotine gum or to nicotine patch, the results of the studies showed that the efficacy of combined therapy was no better than that of monotherapy. Thus, combined therapy should be prescribed with caution because the evidence is scarce, and the adverse effects are unknown.

A review of three RCTs (N = 2,841) addressing the effect of pay or incentives on the efficacy of smoking cessation showed that financial reimbursement and financial incentives had a positive impact on pharmacotherapy. However, the efficacy of free distribution of nicotine patch was not better than that of nicotine patch purchased over the counter. The systematic review and meta-analysis by Reda et al. (2009)<sup>346</sup> reviewed nine RCTs and controlled trials (CTs), and concluded that full financial coverage compared with no coverage could increase the quit rates, quit attempts, and utilization of pharmacotherapy. Because cost is a barrier to access to smoking cessation medication, coverage should be considered in treatment strategies.

Evidence is limited for populations such as adolescents, pregnant women, and those with low income, cancer, or stress disorders. For adolescents, the results of two RCTs of pharmacological interventions (patch versus gum versus placebo [N = 120], and patch plus bupropion versus patch [N = 211]) failed to detect an effect of using drugs for smoking cessation in youth. Similar findings were reported by Grimshaw and Stanton (2008).<sup>347</sup> In pregnant women, two RCTs (patch versus placebo [N = 250], and gum versus placebo [N = 194]) failed to detect the efficacy of the drugs over placebo. Also, no difference between groups was obtained in the study comparing patch plus behaviour support versus behaviour support (N = 181). The systematic review by Smith et al. (2006),<sup>348</sup> with limited evidence on pregnancy, had similar findings. Evidence on pharmacotherapy interventions to help low-income smokers (two RCTs), cancer patients (one RCT), and those with stress disorders (one RCT) is scarce. Findings from the studies showed a lack of efficacy of pharmacotherapy. The success rates were often low, indicating inappropriate treatment strategies. The efficacies of NRT in those populations are unclear, and the data on bupropion and varenicline are limited.

The populations that showed resistance to using pharmacotherapies were smokers with substance abuse disorders, mental disorders, and depression. Of the four trials that assessed the efficacy of pharmacotherapy in substance abuse smokers including those who were alcohol dependent and methadone-maintained, one trial (N = 115) showed that nicotine patch is better than placebo in helping smokers with a history of alcohol dependence stop smoking. The other trials did not find any intervention effects of NRT or behavioural support for smoking cessation in methadone-

maintained or alcohol dependent smokers. Prochaska et al. (2004),<sup>349</sup> in reviewing 19 RCTs, observed that the intervention effects for smoking cessation were significant at post-treatment, but they were non-significant at long-term follow-up. For those with mental disorders including schizophrenia, none of the six included trials with a total population of 510 showed any effect of NRT, bupropion, or NRT plus bupropion in helping these patients stop smoking. The efficacy of NRT (gum, patch) or bupropion for smoking cessation in smokers with a history of depression is unclear. Together, given that the interventions among trials were heterogeneous, the intervention effects for smoking cessation in these populations are uncertain.

Some interventions were found to be better than others in cessation treatment for smokers with cardiovascular or smoking-related diseases, COPD, or for hospitalized smokers. In five trials (N = 1,673) assessing five different interventions for smoking cessation in smokers with cardiovascular or smoking-related diseases, nicotine gum, nicotine patch, and bupropion were shown to be superior compared with placebo, in up to 12 months of follow-up. The addition of behavioural support to nicotine patch, however, did not increase the drug's efficacy. Nicotine patch plus nicotine inhaler plus bupropion was better than nicotine patch. For patients with COPD, nicotine sublingual (one trial, N = 370) and bupropion (two trials, N = 579) were superior to placebo. The meta-analytic review of van der Meer et al. (2008)<sup>350</sup> found that a combination of psychosocial interventions and pharmacological interventions (NRT or bupropion) is superior to no treatment or psychosocial intervention alone in COPD patients. While this report was being reviewed, a trial<sup>53</sup> comparing the efficacy of varenicline with placebo showed that varenicline was effective for smoking cessation in smokers with cardiovascular disease. It was also found that varenicline was well-tolerated and did not increase cardiovascular events or mortality. Tashkin et al. (2009)<sup>351</sup> reported at a conference meeting that varenicline had a significant smoking abstinence effect compared to placebo in mild-to-moderate COPD patients. Thus, NRT, bupropion, or varenicline could be used as an aid in smoking cessation to smokers with cardiovascular diseases or COPD.

For hospitalized patients, 13 trials assessed five different interventions, including pharmacotherapy and behavioural support. The heterogeneous nature of the populations and the interventions, together with the contradictory results between studies, disallowed a pooling of the point estimates. Nicotine patch (two trials, N = 358) and bupropion (two trials, N = 331) were not better than placebo in helping hospitalized patients quit smoking. Adding minimal counselling to nicotine patch did not improve long-term effects compared with nicotine patch alone (one trial, N = 209) or counselling alone (one trial, N = 245). Our findings agreed with those of Rigotti et al. (2008).<sup>352</sup> Compared with usual care, adding behavioural support to NRT was found to be efficacious in three trials (N = 691) and to have no effect in three other trials (N = 1,740). The systematic review of Cropley et al. (2008),<sup>353</sup> while assessing interventions (including counselling, counselling plus NRT, or bupropion) versus usual care, found that the effects seem to be short-lived. Two systematic reviews and meta-analyses by Mufano et al. (2001)<sup>354</sup> and Rigotti et al. (2008)<sup>352</sup> arrived at the same conclusion that high-intensity behavioural interventions with at least one month of follow-up contact, irrespective of whether NRT was used, are effective in promoting smoking cessation among hospitalized patients. Thus, behavioural support with follow-up contact after patients' discharges from the hospital may play a role in pharmacotherapy treatment for smoking cessation.

### 10.3.2 Economic

The generalizability of our economic analyses is limited to the populations being studied; i.e., general population, those with cardiovascular or other smoking-related diseases, and hospitalized patients. This is because of the varying efficacy of smoking cessation interventions across populations. Moreover, the overall structure of economic models may vary across populations. For example, assessing the cost-effectiveness of smoking cessation interventions targeting pregnant women may require incorporating the potential effects of smoking cessation on a mother and her children. Therefore, the results in this report are not necessarily transferable for deriving implications in other populations.

Except for models targeting general population, where the cost-effectiveness of all the pharmacological interventions of our interest (NRT [gum, patch, inhaler, and lozenge], bupropion, and varenicline) was assessed, the generalizability of cost-effectiveness results for other models were limited to the specific interventions that were considered. For example, in the cost-effectiveness analyses of adding behavioural interventions, only nicotine patch and telephone counselling were considered. Therefore, the results are not generalizable to other types of pharmacological or behavioural interventions. Similarly, the cost-effectiveness results of paying or copaying for pharmacotherapies were limited to NRT (gum, patch, and inhaler) and bupropion. The results for cardiovascular or smoking-related disease populations are only generalizable to NRT (gum, patch, and inhaler) and bupropion, and the results for the hospitalized population are only generalizable to nicotine patch and bupropion.

The perspective of the economic analyses was that of a publicly funded health care system. Therefore, the results do not reflect a wider perspective, such as a societal perspective. A publicly funded health care system perspective was chosen for several reasons. First, the perspective reflected the target audience of the report (a jurisdictional health care system). Therefore, direct costs were most relevant. Second, the methods for estimating indirect costs (such as productivity loss) are still under development. Therefore, the inclusion of indirect costs would impose further uncertainty on the cost-effectiveness results. If an even broader perspective was chosen, such as inclusion of impacts of tax revenue or lost employment opportunities due to smoking, then the valuation of these factors can be even more difficult. With a narrower perspective, the costs are more accurately valued while also reflecting a drug plan's decision perspective. An implication of including indirect costs in the analyses is that it may result in the ICER estimates to be more favourable to the intervention drugs because productivity loss and other indirect costs to the society would be avoided through smoking cessation interventions. These additional savings were not considered in our analyses.

In all models, efforts were made to find parameter values based on Canadian data. However, not all the parameters regarding relative risks associated with chronic conditions, utilities, and transition probabilities were based on a Canadian source. Therefore, the generalizability of these parameter values was assumed in our economic models.

The results on the cost-effectiveness of paying or copaying for pharmacological interventions showed that the expected value of conducting additional research on this was small compared with other models considered in this report. However, efficacy data were based on one study<sup>195</sup> that was conducted in The Netherlands. Therefore, although it seems clear that full

reimbursement is cost-effective, the external validity may be a concern. Unless Canadian studies assessing the impacts of paying or copaying for pharmacological interventions are conducted, the generalizability of our model to the Canadian setting is unknown.

The results of the budget impact analyses are not generalizable to jurisdictions that were not considered in this report. This is because the current and predicted number of claims and total expenditures depend on population size and the proportion of smokers who are eligible for reimbursement, which could differ considerably across jurisdictions.

## **10.4 Knowledge Gaps**

### **10.4.1 Clinical**

While reviewing the efficacy of pharmacotherapy interventions for smoking cessation, some knowledge gaps were identified. This review only covers NRT, bupropion, and varenicline, while alternatives such as vaccine and pharmacogenetic approaches may have future potential. Although varenicline has been shown to be efficacious for smoking cessation in the general adult population, the evidence of its effect in specific populations is lacking. The evidence of head-to-head comparisons between pharmacotherapies is limited, especially between NRT. Therefore, it is difficult to be certain which drug is better than the others. There is a need for consensus about cessation rates to make the comparisons of studies more meaningful. In some trials, six- and 12-month CAR are usual primary study end points, and six- and 12-month seven-day PPA are usual secondary study end points. Smoking cessation interventions need to be further developed and tailored to each specific population, including adolescents, pregnant women, and those with low income, cancer, stress disorder, substance abuse, mental disorder or depression. The use of interventions needs to be sensitive to clinical circumstances, and dosages need to reflect differing metabolic and physiologic realities. More research is needed in head-to-head comparisons of drug versus drug plus behavioural support in the general and specific populations. The behavioural support could be tailored to each population to maximize the efficacy of the pharmacotherapy. The follow-up in most hospital studies was very limited after discharge that usually limited the usefulness of long-term therapy. For the feasible implementation of an intervention in daily practice, resources, planning, and accountability could be considered in addition to the evidence of clinical and economic effectiveness.

### **10.4.2 Economic**

Based on our cost-effectiveness analyses, knowledge gaps were identified in several areas. First, because of a lack of clinical evidence, our economic models (except the model targeting a general population) were limited to comparisons of a few types of pharmacological interventions. Therefore, the lack of clinical evidence prevented the assessment of cost-effectiveness among all the pharmacological interventions available in the Canadian market.

Second, a lack of clinical evidence on the efficacy of adding behavioural interventions limited our economic analyses to one type of behavioural intervention (i.e., telephone counselling). Therefore, additional direct or indirect evidence would help in conducting further analyses comparing the cost-effectiveness of adding different types of behavioural interventions to a common pharmacological intervention.

Third, as long as a decision maker was willing to spend at least \$10,143 per QALY gained, bupropion was the optimal treatment choice. However, it is important to note that the role of pharmacotherapy among hospitalized smokers is management of withdrawal and long-term quit. Although bupropion and varenicline have a role in outpatients, they have not been tested for acute withdrawal. Therefore, the role of NRT is important for inpatients because NRT has been shown to work in acute nicotine withdrawal, which is often precipitated by admission to hospital when access to cigarettes is restricted. Further analysis of inpatient-outpatient variations in cost-effectiveness would be warranted.

Finally, our value of information analyses showed that evidence on clinical efficacy is the major driving factor in the overall decision uncertainty. This implies that conducting further research to obtain more accurate clinical efficacy data would reduce our expected cost of making incorrect decisions. Among various types of economic models that were assessed in this report, the knowledge gap associated with the cost-effectiveness of treating specific populations seemed to be the greatest, making it more valuable to conduct additional research targeting specific populations than to focus future research on a general population.

## 11 CONCLUSIONS

Given the available evidence, all pharmacotherapies that are reviewed are efficacious in helping the general population quit smoking, with varenicline being superior to bupropion and conventional use of nicotine patch. Adding behavioural support to bupropion, nicotine patch or nicotine gum seems to have little impact on overall abstinence rates. Mixed or limited evidence was found on the effective regimens of pharmacotherapies or combined therapies of drugs and behavioural support programs in specific populations. More research is needed in the development of more effective interventions for certain specific populations, considering clinical circumstances, barriers, and inequalities in the delivery of smoking cessation treatment.

A review of relevant literature suggests that cost is a barrier: full coverage may increase the uptake of cessation therapies and have an impact on use and success rates. An enhanced infrastructure, including additional training of health professionals and the development and application of systematic approaches to cessation in all professional settings, will enhance our ability to assist with smoking cessation and derive health and economic benefits that follow.

For pharmacological interventions targeting a general population, bupropion and varenicline were dominating options (cost less and more effective) over nicotine gum, patch, lozenge, and inhaler. The analysis indicated that if a provider's willingness to pay was greater than \$10,000 per QALY, then varenicline was preferred.

It must be emphasized, however, that clinical considerations (health states and contraindications) and clinical responses (side effects) are likely to be important determinants of the choice of pharmacotherapy. It would also be a mistake to assume that the use one medication should prevail or be favoured in any clinical situation or diagnostic category. The value of information analyses indicated that quit rates were the major source of overall decision uncertainty. Overall decision uncertainty was greater for economic models targeting special populations than other

models considered. Further research to obtain more accurate estimates on the clinical efficacy of smoking cessation interventions would provide information value; this would be particularly valuable for assessing specific populations.

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# APPENDIX 1: LITERATURE SEARCH STRATEGY

<b>OVERVIEW</b>	
<b>Literature Search Strategy for Clinical and Cost-effectiveness Studies</b>	
Interface:	Ovid
Databases:	BIOSIS Previews < 1985 to 1989 > and < 1989 to end of alerts > EMBASE < 1980 to end of alerts > Ovid Medline < 1950 to end of alerts > Ovid Medline In-Process & Other Non-Indexed Citations < current to end of alerts > PsycINFO <1967 to end of alerts > <b>Note:</b> Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 2009
Alerts:	Monthly search updates beginning February 2009 and running until end of March 2010.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials; also costs and cost analysis studies, quality of life studies, and economic literature.
Limits:	Publication years – no limit Humans (for clinical search)
<b>SYNTAX GUIDE</b>	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.cb	Chemicals & biochemicals
.tw	Text word
.mp	Mapped word
.po	Population group
.md	Methodology
.jw	Journal word
.sh	Subject heading
ec	Economics (MeSH subheading)

## MULTI-DATABASE STRATEGY

Line #	Strategy
	<b>Drugs Under Review</b>
1	(varenicline or champix or chantix).ti,ab,hw.
2	(cp adj ("52655*" or "526,555")).ti,ab,hw.
3	(249296-44-4 or 375815-87-5).rn,cb.
4	or/1-3
5	(bupropion or amfebutamone or zyban or bupropion or wellbutrin).ti,ab,hw.
6	(quomen or zyntabac).ti,ab,hw.
7	((brn adj "2101062") or brn2101062 or (BW adj "323") or bw323 or (BW adj 323u66) or BW323u66).ti,ab,hw.
8	(34911-55-2 or 34841-39-9 or 31677-93-7 or 34911-55-2).rn,cb.
9	or/5-8
10	nicotine replacement.ti,ab,hw.
11	(nrt and (smoking or smokers or smoker or smoke or tobacco or nicotine or cigarette* or cessation)).ti,ab,hw.
12	(nicotine polacrilex or nicorette or prostep or nicotrol or nicoderm or niquitin or nicabate or nicotinell or habitrol).ti,ab,hw.
13	((commit or thrive) adj3 (nicotine or lozenge* or gum* or nrt)).ti,ab.
14	(nicotine adj3 (gum* or lozenge* or patch* or transdermal or nasal spray* or intranasal spray* or tablet* or inhaled or inhaler or inhalers or inhalator* or inhalation*)).ti,ab.
15	(nicotine adj (gum* or lozenge* or patch* or transdermal or nasal spray* or intranasal spray* or tablet* or inhaled or inhaler or inhalers or inhalator* or inhalation*)).hw.
16	96055-45-7.rn,cb.
17	or/10-16
18	smoking cessation.ti,ab,hw.
19	"tobacco use disorder".ti,ab,hw.
20	smoking/ or nicotine/ or tobacco/ or cigarette smoking/ or tobacco smoking/
21	tobacco dependence/ or nicotine withdrawal/ or tobacco abuse control/ or "tobacco use cessation"/
22	(smoking or smokers or smoker or smoke or tobacco or nicotine or cigarette*).ti,ab.
23	or/18-22
24	4 or 17 or (9 and 23)
	<b>Methodology filter: Clinical Trials</b>
25	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
26	Randomized Controlled Trial/
27	Randomized Controlled Trials as Topic/
28	Controlled Clinical Trial/
29	Controlled Clinical Trials as Topic/
30	Randomization/

## MULTI-DATABASE STRATEGY

31	Random Allocation/
32	Double-Blind Method/
33	Double Blind Procedure/
34	Double-Blind Studies/
35	Single-Blind Method/
36	Single Blind Procedure/
37	Single-Blind Studies/
38	Placebos/
39	Placebo/
40	Control Groups/
41	Control Group/
42	(random* or sham or placebo*).ti,ab,hw.
43	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
44	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
45	(control* adj3 (study or studies or trial*)).ti,ab,hw.
46	(Nonrandom* or non random* or non-random* or quasi-random*).ti,ab,hw.
47	(allocated adj1 to).ti,ab,hw.
48	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
49	Clinical Trial.pt.
50	Clinical Trials as Topic/
51	trial.ti.
52	or/25-51
	<b>Clinical Studies Results</b>
53	24 and 52
	<b>Methodology filter: Systematic Reviews</b>
54	meta-analysis.pt.
55	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
56	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
57	((quantitative adj3 (review* or overview* or synthes*) or (research adj3 (integrati* or overview*))).ti,ab.
58	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
59	(data synthes* or data extraction* or data abstraction*).ti,ab.
60	(handsearch* or hand search*).ti,ab.
61	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
62	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
63	(meta regression* or metaregression* or mega regression*).ti,ab.
64	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

**MULTI-DATABASE STRATEGY**

65	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
66	(cochrane or health technology assessment or evidence report).jw.
67	(meta-analysis or systematic review).md.
68	or/54-67
	<b>Systematic Reviews Results</b>
69	24 and 68
	<b>Clinical Studies/Systematic Reviews Results</b>
70	53 or 69
	<b>Human Filter</b>
71	exp animals/
72	exp animal experimentation/
73	exp models animal/
74	exp animal experiment/
75	nonhuman/
76	exp vertebrate/
77	animal.po.
78	or/71-77
79	exp humans/
80	exp human experiment/
81	human.po.
82	or/79-81
83	78 not 82
	<b>Final Clinical Results</b>
84	70 not 83
	<b>Economic Studies Results</b>
85	*Economics/
86	*Economics, Medical/
87	*Economics, Pharmaceutical/
88	exp "Costs and Cost Analysis"/
89	exp Health Care Costs/
90	exp decision support techniques/
91	economic value of life.sh.
92	exp models, economic/
93	markov chains.sh.
94	monte carlo method.sh.
95	uncertainty.sh.
96	quality of life.sh.

## MULTI-DATABASE STRATEGY

97	quality-adjusted life years.sh.
98	exp health economics/
99	exp economic evaluation/
100	exp pharmacoeconomics/
101	exp economic aspect/
102	quality adjusted life year/
103	quality of life/
104	exp "costs and cost analyses"/
105	cost containment.sh.
106	(economic impact or economic value or pharmacoeconomics or health care cost or economic factors or cost analysis or economic analysis or cost or cost-effectiveness or cost effectiveness or costs or health care cost or cost savings or cost-benefit analysis or hospital costs or medical costs or quality-of-life).sh.
107	health resource allocation.sh.
108	(econom* or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget* or afford* or pharmacoeconomic* or pharmaco-economic*).ti.
109	(decision adj1 (tree* or analy* or model*)).ti,ab.
110	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).ti,ab.
111	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales or qald or qtime or daly or haly or hale or euroqol or eq5d or eq-5d or hql or hqol or h-qol or hrqol or hr-qol or hye or hyes).ti,ab.
112	(sensitivity analysis or sensitivity analyses or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc* or disability adjusted life or health adjusted life).ti,ab.
113	(unit cost* or drug cost* or hospital cost* or health care cost* or medical cost*).ti,ab.
114	(economic evaluation* or economic review*).tw.
115	(cost* adj2 (util* or effectiveness or efficac* or benefit* or consequence* or analy* or minimi*)).ti,ab.
116	(markov* or monte carlo).ti,ab.
117	(health adj2 (indicator* or status or utilit*)).ti,ab.
118	hui.ti.
119	((utilit* adj2 (valu* or measure*)) or (time adj2 trade)).ti.
120	or/85-119
121	24 and 120
122	*smoking cessation/ec or *"tobacco use disorder"/ec or *"tobacco use cessation"/ec
123	121 or 122
	<b>Additional Economic Search for Smoking Cessation Models</b>
124	*smoking cessation/
125	*"tobacco use disorder"/ or *tobacco dependence/ or *"tobacco use cessation"/ or *nicotine withdrawal/ or *tobacco abuse control/ or *nicotinic agonists/ or *nicotinic receptor blocking agents/
126	((smoking or smokers or smoker or smoke or tobacco or nicotine or cigarette*) adj2 (cessation or dependen* or withdrawal or abuse or quit* or stop* or decreas* or reduc* or cease* or disorder* or cut* down)).ti.

## MULTI-DATABASE STRATEGY

127	or/124-126
128	model*.ti,hw.
129	127 and 128
130	((smoking or smokers or smoker or smoke or tobacco or nicotine or cigarette*) adj2 (cessation or dependen* or withdrawal or abuse or quit* or stop* or decreas* or reduc* or cease* or disorder* or cut* down) adj4 model*).ab.
131	129 or 130
132	120 and 131
	<b>Question 11 (Willingness to Pay)</b>
133	smoking cessation.hw.
134	"tobacco use disorder"/ or tobacco dependence/ or "tobacco use cessation"/ or nicotine withdrawal/ or tobacco abuse control/ or nicotinic agonists/ or nicotinic receptor blocking agents/
135	((smoking or smokers or smoker or smoke or tobacco or nicotine or cigarette*) adj2 (cessation or dependen* or withdrawal or abuse or quit* or stop* or decreas* or reduc* or cease* or disorder* or cut* down)).ti.
136	((smoking or tobacco or nicotine) adj2 (cessation or dependen* or withdrawal or abuse or disorder*)).ab.
137	or/133-136
138	(willing* adj5 (pay* or co-pay*)).ti,ab,hw.
139	(24 or 137) and 138
	<b>Question 12 (Equitable Access and Accountability)</b>
140	(program* or service* or intervention* or initiative* or support or project* or clinic or clinics).ti,ab,hw.
141	(plan* or implement* or initiat* or start* or design* or deliver* or creat* or manage or manages or managing).ti,ab,hw.
142	140 and 141
143	program development/ or program evaluation/
144	142 or 143
145	(access or accessib* or accountab* or fund* or responsibility or equity or equitab* or inequalit* or socioeconomic* or socio-economic* or disparit* or equalit* or fairness or ethnic* or gender or elderly or demographic* or sociodemographic* or geograph* or social class or minority group* or educational status or mental disorder* or mental illness* or mentally ill).ti,ab,hw.
146	exp ethnic groups/ or exp social class/ or social responsibility/ or exp demography/ or exp gender identity/ or exp geography/ or exp minority groups/ or exp sex factors/ or exp age factors/ or exp educational status/ or exp socioeconomic factors/ or exp responsibility/ or exp sex differences/ or exp health care utilization/ or exp socioeconomics/ or (exp mental disorders/ not "tobacco use disorder"/)
147	145 or 146
148	144 and 147
149	health services accessibility/ or health care access/
150	148 or 149
151	24 and 150

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per Medline search, with appropriate syntax used.
Health Economic Evaluations Database (HEED)	Same keywords used as per Medline search. Syntax adjusted for HEED database. Used for economic searches only.
Cumulative Index to Nursing & Allied Health Literature (CINAHL)	Same MeSH (plus CINAHL subject headings), keywords, limits, and study types used as per Medline search. Syntax adjusted for CINAHL database searched through EBSCOhost. Used for clinical searches only.
Cochrane Library	Same MeSH and keywords used as per Medline search, with appropriate syntax used.
Centre for Reviews and Dissemination (CRD) databases	Same MeSH and keywords used as per Medline search, with appropriate syntax used.

## Grey Literature and Hand Searches

Dates for Search:	February 2009 [limited update: November 2009]
Keywords:	Included terms for varenicline (Champix, Chantix), bupropion (Zyban), nicotine replacement therapy (NRT), and smoking/tobacco cessation.
Limits:	No limits

**NOTE:** This section lists the main agencies, organizations, and websites searched; **it is not a complete list.** For a complete list of sources searched, contact CADTH (<http://www.cadth.ca>).

### Health Technology Assessment Agencies

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS). Québec  
<http://www.aetmis.gouv.qc.ca>

Canadian Agency for Drugs and Technologies in Health (CADTH)  
<http://www.cadth.ca>

Centre for Evaluation of Medicines. Father Sean O'Sullivan Research Centre,  
 St. Joseph's Healthcare, Hamilton, and McMaster University, Faculty of Health Sciences. Hamilton, Ontario  
<http://www.thecem.net/>

Centre for Health Services and Policy Research, University of British Columbia  
<http://www.chspr.ubc.ca/cgi-bin/pub>

Health Quality Council. Saskatchewan.  
<http://www.hqc.sk.ca/>

Institute for Clinical Evaluative Sciences (ICES). Ontario  
<http://www.ices.on.ca/>

Institute of Health Economics (IHE). Alberta  
<http://www.ihe.ca/>

Manitoba Centre for Health Policy (MCHP)  
<http://umanitoba.ca/medicine/units/mchp/>

Ontario Ministry of Health and Long Term Care. Health Technology Analyses and Recommendations  
[http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas\\_mn.html](http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas_mn.html)

The Technology Assessment Unit of the McGill University Health Centre  
<http://www.mcgill.ca/tau/>

Therapeutics Initiative. Evidence-Based Drug Therapy. University of British Columbia  
<http://www.ti.ubc.ca>

Health Technology Assessment International (HTAi)  
<http://www.htai.org>

International Network for Agencies for Health Technology Assessment (INAHTA)  
<http://www.inahta.org>

WHO Health Evidence Network  
<http://www.euro.who.int/HEN>

Centre for Clinical Effectiveness, Southern Health  
[http://www.southernhealth.org.au/page/Health\\_Professionals/CCE/](http://www.southernhealth.org.au/page/Health_Professionals/CCE/)

NPS RADAR (National Prescribing Service Ltd.)  
[http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive\\_alpha.html](http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html)

Institute of Technology Assessment (ITA)  
<http://www.oeaw.ac.at/ita/index.htm>

Federal Kenniscentrum voor de Gezondheidszorg  
<http://www.kenniscentrum.fgov.be>

Danish Centre for Evaluation and Health Technology Assessment (DACEHTA). National Board of Health  
<http://www.sst.dk/english/dacehta.aspx>

DSI Danish Institute for Health Services Research  
[http://www.dsi.dk/frz\\_about.htm](http://www.dsi.dk/frz_about.htm)

Finnish Office for Health Care Technology and Assessment (FinOHTA). National Research and Development Centre for Welfare and Health  
<http://finohta.stakes.fi/EN/index.htm>

Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT)  
[http://cedit.aphp.fr/english/index\\_present.html](http://cedit.aphp.fr/english/index_present.html)

German Institute for Medical Documentation and Information (DIMDI). Federal Ministry of Health  
<http://www.dimdi.de/static/de/hta/db/index.htm>

Health Service Executive  
<http://www.hse.ie/en/>

College voor Zorgverzekering/Health Care Insurance Board (CVZ)  
<http://www.cvz.nl>

Health Council of the Netherlands  
<http://www.gezondheidsraad.nl/>

New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)  
<http://nzhta.chmeds.ac.nz/>

Norwegian Centre for Health Technology Assessment (SMM)  
<http://www.kunnskapsenteret.no/>

Instituto de Salud Carlos III / Healthcare Technology Evaluation Agency  
[http://www.isciii.es/htdocs/investigacion/Agencia\\_quees.jsp](http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp)  
Catalan Agency for Health Technology Assessment and Research (CAHTA)  
<http://www.gencat.net/salut/depsan/units/aatrm/html/en/Du8/index.html>

CMT - Centre for Medical Technology Assessment  
<http://www.cmt.liu.se/?l=sv>

Swedish Council on Technology Assessment in Health Care (SBU)  
<http://www.sbu.se/>

Swiss Network for Health Technology Assessment  
<http://www.snhta.ch/>

European Information Network on New and Changing Health Technologies (EUROSCAN). University of Birmingham. National Horizon Scanning Centre  
<http://www.euroscan.bham.ac.uk>

National Horizon Scanning Centre (NHSC)  
<http://www.pcpoh.bham.ac.uk/publichealth/horizon>

National Institute for Health Research, NIHR Health Technology Assessment programme  
<http://www.hta.ac.uk/>

NHS National Institute for Clinical Excellence (NICE)  
<http://www.nice.org.uk>

NHS Quality Improvement Scotland  
<http://www.nhshealthquality.org>

University of York NHS Centre for Reviews and Dissemination (NHS CRD)  
<http://www.york.ac.uk/inst/crd>

Agency for Healthcare Research and Quality (AHRQ)  
<http://www.ahrq.gov/>

Dept. of Veterans Affairs Research & Development, general publications  
<http://www.research.va.gov/resources/pubs/default.cfm>

VA Technology Assessment Program (VATAP)  
<http://www.va.gov/vatap/>

ECRI  
<http://www.ecri.org/>

Institute for Clinical Systems Improvement  
<http://www.icsi.org/index.asp>

Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC)  
<http://www.bcbs.com/blueresources/tec/tec-assessments.html>

University HealthSystem Consortium (UHC)  
<http://www.uhc.edu/>

### **Health Economic**

Bases Codecs. CODECS (COonnaissances et Décision en EConomie de la Santé) Collège des Economistes de la Santé/INSERM  
<http://infodoc.inserm.fr/codecs/codecs.nsf>

Centre for Health Economics and Policy Analysis (CHEPA). Dept. of Clinical Epidemiology and Biostatistics. Faculty of Health Sciences. McMaster University, Canada  
<http://www.chepa.org>

Health Economics Research Group (HERG). Brunel University, U.K.  
<http://www.brunel.ac.uk/about/acad/herg>

Health Economics Research Unit (HERU). University of Aberdeen  
<http://www.abdn.ac.uk/heru/>

The Hospital for Sick Children (Toronto). PEDE Database  
<http://pede.ccb.sickkids.ca/pede/database.jsp>

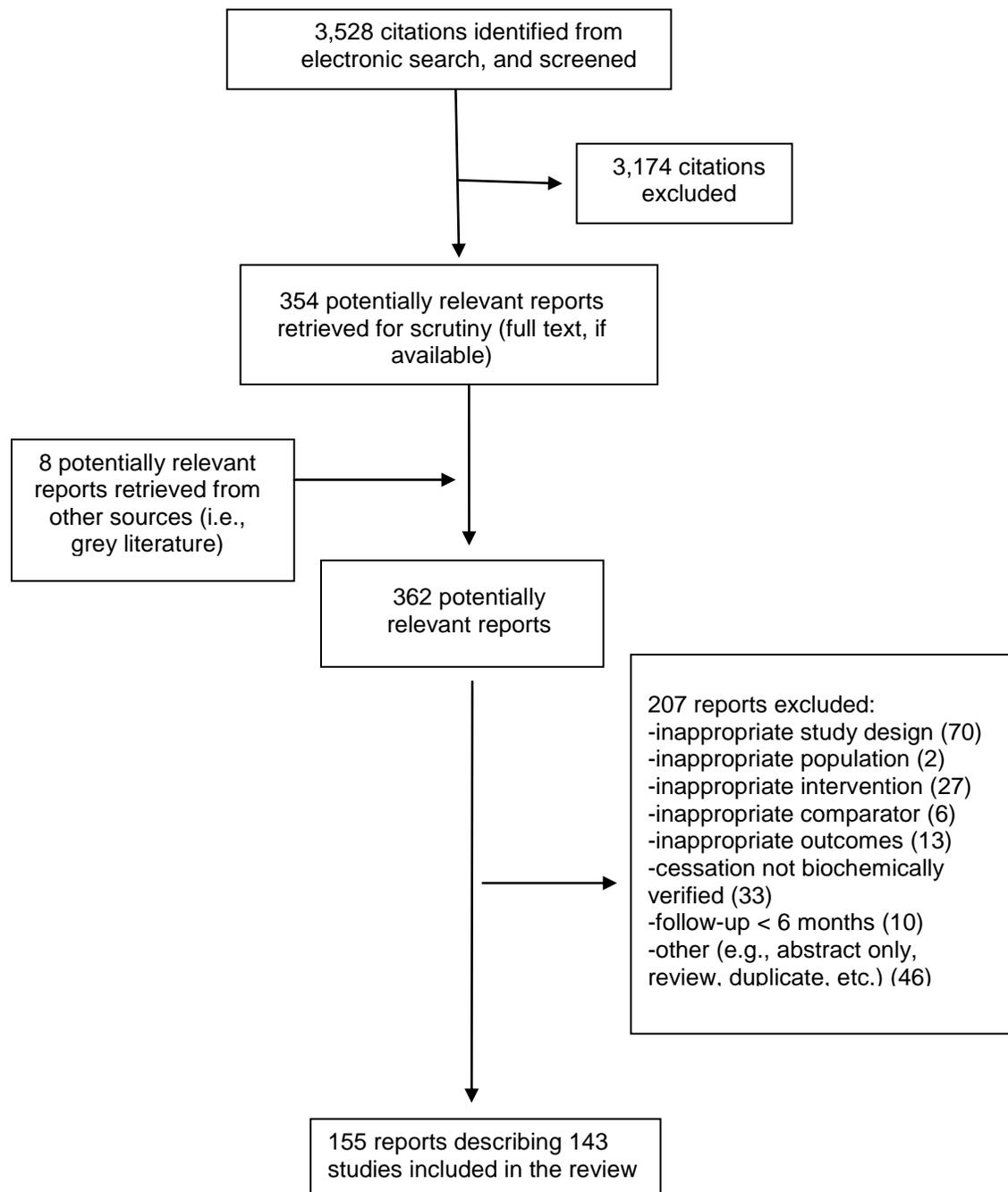
University of Connecticut. Department of Economics. RePEc database  
<http://ideas.repec.org>

### **Search Engines**

Google  
<http://www.google.ca/>

MSN Live Search (Bing)  
<http://www.msn.com>

## APPENDIX 2: SELECTED REPORTS FOR CLINICAL REVIEW



# APPENDIX 3: DATA EXTRACTION FORM AND QUALITY ASSESSMENT FOR CLINICAL-EFFECTIVENESS STUDIES

EXTRACTOR'S NAME:

<b>Study</b>				
First author, year of publication, (REFID)				
<b>Study Characteristics</b>				
Objective				
Population type				
Publication type	Journal			
Sponsor				
Countries				
No of centres				
Study design	RCT			
Comparison arms				
Description of intervention and comparator				
Length of follow-up (months)				
Patients assigned, No.				
Patients completed trials, No.				
Withdrawals, No.				
Intention-to-treat (yes/no)				

<b>Quality assessment</b>	
<b>Author, year (REFID)</b>	<b>Score</b>
<b>Study design</b>	
1. Large RCT (Over 50 in each arm): 5 points	
2. Small RCT: 3 points	
3. Prospective: 2 points	
4. Retrospective: 1 point	
If RCT*:	
a. Randomization appropriately described?	
b. Blinded?	
c. Blinding appropriately described?	
* An RCT gets full points if addressed all 3 characteristics. Half a point is deducted for each characteristic not addressed.	
<b>Study performance</b>	
Score (Info missing 0 point, Info limited 1 point, Info satisfactory 2 points)	
1. Patient selection	
2. Description/specification of the intervention	
3. Specification and analysis of study (intention-to-treat)	

<b>Quality assessment</b>	
4. Patient disposal	
5. Outcomes reported	
<b>Overall Score</b>	
<b>Category</b>	
A (overall score 11.5-15.0): High quality – high degree of confidence in study findings B (overall score 9.5-11.0): Good quality – some uncertainty regarding the study findings C (overall score 7.5-9.0): Fair to good quality – some limitations that should be considered in any implementation of study findings D (overall score 5.5-7.0): Poor to fair quality – substantial limitations in the study; findings should be used cautiously E (overall score 1-5.0): Poor quality – unacceptable uncertainty for study findings	

<b>Patient baseline characteristics</b>				
Comparison arms				
Inclusion				
Exclusion				
Age (y), mean ± SD				
Gender, male/female (%)				
BMI (kg/m <sup>2</sup> )				
Medical history (description)				
Duration of smoking (years), mean ± SD				
Cigarettes smoked per day, No.				
Willingness to quit (yes/no)				
<b>Outcomes</b>				
Comparison arms				
Patients considered for outcomes, No.				
Abstinence rate (%)				
Continuous				
• 6 mth				
• 1 yr				
• >1 yr				
Prolonged				
• 6 mth				
• 1 yr				
• >1 yr				
7-day point prevalence				
• 6 mth				
• 1 yr				
• >1 yr				
All adverse events, No.				

## APPENDIX 4: INCLUDED STUDIES FOR QUESTIONS 1-4, 11, 12

### Appendix 4a: For questions 1-4

#### A. Varenicline

First author	Reference
<b>Varenicline versus placebo (6)</b>	
Nakamura (2007) <sup>47</sup>	Nakamura M, Oshima A, Fujimoto Y, Maruyama N, Ishibashi T, Reeves KR. Efficacy and tolerability of varenicline, an a4b2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers. <i>Clin Ther</i> 2007;29(6):1040-56.
Niaura (2008) <sup>48</sup>	Niaura R, Hays JT, Jorenby DE, Leone FT, Pappas JE, Reeves KR, et al. The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial. <i>Curr Med Res Opin</i> 2008;24(7):1931-41.
Oncken (2006) <sup>49</sup>	Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. <i>Arch Intern Med</i> 2006;166(15):1571-7.
Tsai (2007) <sup>50</sup>	Tsai ST, Cho HJ, Cheng HS, Kim CH, Hsueh KC, Billing CB, et al. A randomized, placebo-controlled trial of varenicline, a selective a4b2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. <i>Clin Ther</i> 2007;29(6):1027-39.
Wang (2009) <sup>51</sup>	Wang C, Xiao D, Chan KP, Pothirat C, Garza D, Davies S. Varenicline for smoking cessation: A placebo-controlled, randomized study. <i>Respirology</i> 2009;14(3):384-92.
Williams (2007) <sup>52</sup>	Williams KE, Reeves KR, Billing CB, Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. <i>Curr Med Res Opin</i> 2007;23(4):793-801.
<b>Varenicline versus patch (1)</b>	
Aubin (2008) <sup>57</sup>	Aubin HJ, Bobak A, Britton JR, Oncken C, Billing CB, Jr., Gong J, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. <i>Thorax</i> 2008;63(8):717-24.
<b>Varenicline versus bupropion versus placebo (3)</b>	
Gonzales (2006) <sup>54</sup>	Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an a4b2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. <i>JAMA</i> 2006;296(1):47-55.
Jorenby (2006) <sup>55</sup>	Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an a4b2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. <i>JAMA</i> 2006;296(1):56-63.
Nides (2006) <sup>56</sup>	Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, et al. Smoking cessation with varenicline, a selective a4b2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. <i>Arch Intern Med</i> 2006;166(15):1561-8.

## B. Nicotine replacement therapy (NRT) versus placebo

First author	Reference
<b>Nicotine patch versus placebo (23)</b>	
Campbell (1996) <sup>71</sup> (hospitalized)	Campbell IA, Prescott RJ, Tjeder-Burton SM. Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study. <i>Respir Med</i> 1996;90(1):47-51.
Davidson (1998) <sup>58</sup>	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. <i>Arch Fam Med</i> 1998;7(6):569-74.
Daughton (1991) <sup>59</sup>	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. <i>Arch Intern Med</i> 1991;151(4):749-52.
Daughton (1998) <sup>60</sup>	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. <i>Arch Fam Med</i> 1998;7(5):425-30.
Fiore (1994) <sup>61</sup>	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. <i>Chest</i> 1994;105(2):524-33.
Glavaš (2003) <sup>75</sup>	Glavaš D, Rumboldt M, Rumboldt Z. Smoking cessation with nicotine replacement therapy among health care workers: randomized double-blind study. <i>Croat Med J</i> 2003;44(2):219-24.
Hays (1999) <sup>62</sup> <b>II</b>	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. <i>Am J Public Health</i> 1999;89(11):1701-7.
Hughes (2003) <sup>63</sup> (Alcohol)	Hughes JR, Novy P, Hatsukami DK, Jensen J, Callas PW. Efficacy of nicotine patch in smokers with a history of alcoholism. <i>Alcohol Clin Exp Res</i> 2003;27(6):946-54.
Hurt (1994) <sup>64</sup>	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. <i>JAMA</i> 1994;271(8):595-600.
ICR group (1993, 1994, 2003) <sup>72,355,356</sup>	Imperial Cancer Research Fund General Practice Research Group. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomised trial in general practice. <i>BMJ</i> 1993;306(6888):1304-8.  Randomised trial of nicotine patches in general practice: results at one year. Imperial Cancer Research Fund General Practice Research Group. <i>BMJ</i> 1994;308(6942):1476-7.  Yudkin P, Hey K, Roberts S, Welch S, Murphy M, Walton R. Abstinence from smoking eight years after participation in randomised controlled trial of nicotine patch. <i>BMJ</i> 2003;327(7405):28-9.
Killen (1997) <sup>65</sup>	Killen JD, Fortmann SP, Davis L, Varady A. Nicotine patch and self-help video for cigarette smoking cessation. <i>J Consult Clin Psychol</i> 1997;65(4):663-72.
Lewis (1998) <sup>66</sup> (Hospitalized)	Lewis SF, Piasecki TM, Fiore MC, Anderson JE, Baker TB. Transdermal nicotine replacement for hospitalized patients: a randomized clinical trial. <i>Prev Med</i> 1998;27(2):296-303.

First author	Reference
Oncken (2007) <sup>67</sup>	Oncken C, Cooney J, Feinn R, Lando H, Kranzler HR. Transdermal nicotine for smoking cessation in postmenopausal women. <i>Addict Behav</i> 2007;32(2):296-309.
Paoletti (1996) <sup>76</sup>	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. <i>Eur Respir J</i> 1996;9(4):643-51.
Richmond (1994, 1997, 2007) <sup>77,357-359</sup>	Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. <i>Med J Aust</i> 1994;161(2):130-5.  Richmond RL, Kehoe L, de Almeida Neto AC. Effectiveness of a 24-hour transdermal nicotine patch in conjunction with a cognitive behavioural programme: one year outcome. <i>Addiction</i> 1997;92(1):27-31.  Richmond RL, Kehoe L, de Almeida Neto AC. Three year continuous abstinence in a smoking cessation study using the nicotine transdermal patch. <i>Heart</i> 1997;78(6):617-8.  Richmond RL, Kehoe L. Ten-year survival outcome of the nicotine transdermal patch with cognitive behavioural therapy. <i>Aust N Z J Public Health</i> 2007;31(3):282-5.
Russell (1993) <sup>73</sup>	Russell MA, 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. <i>BMJ</i> 1993;306(6888):1308-12.
Sachs (1993) <sup>68</sup>	Sachs DP, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. <i>Arch Intern Med</i> 1993;153(16):1881-90.
Stapleton (1995) <sup>74</sup>	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. <i>Addiction</i> 1995;90(1):31-42.
Tonnesen (1991, 1992), <sup>360,361</sup> Mikkelsen (1994) <sup>78</sup>	Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. <i>N Engl J Med</i> 1991;325(5):311-5.  Tonnesen P, Norregaard J, Sawe U. Two-year outcome in a smoking cessation trial with a nicotine patch. <i>Journal of Smoking-Related Disorders</i> 1992;3(3):241-5.  Mikkelsen KL, Tønnesen P, Nørregaard J. Three-year outcome of two- and three-year sustained abstainers from a smoking cessation study with nicotine patches. <i>Journal of Smoking-Related Disorders</i> 1994;5(2):95-100.
Tonnesen (1999) <sup>80</sup>	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. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. <i>Eur Respir J</i> 1999;13(2):238-46.
TNS group (1991, 1999, 2005) <sup>69,362,363</sup>	Transdermal nicotine for smoking cessation. Six-month results from two multicenter controlled clinical trials. Transdermal Nicotine Study Group. <i>JAMA</i> 1991;266(22):3133-8.  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. <i>Prev Med</i> 1999;28(2):113-8.  Shiffman S, Sweeney CT, Dresler CM. Nicotine patch and lozenge are effective for women. <i>Nicotine Tob Res</i> 2005;7(1):119-27.
Westman (1993) <sup>70</sup>	Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation. A randomized trial with telephone counseling. <i>Arch Intern Med</i> 1993;153(16):1917-23.
Wisborg	Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant

First author	Reference
(2000) <sup>79</sup> (Pregnant)	smokers: a randomized controlled study. <i>Obstet Gynecol</i> 2000;96(6):967-71.
<b>Nicotine gum versus placebo (23)</b>	
Ahluwalia (2006) <sup>81</sup>	Ahluwalia JS, Okuyemi K, Nollen N, Choi WS, Kaur H, Pulvers K, et al. The effects of nicotine gum and counseling among African American light smokers: a 2 x 2 factorial design. <i>Addiction</i> 2006;101(6):883-91.
Areechon (1988) <sup>99</sup>	Areechon W, Punnotok J. Smoking cessation through the use of nicotine chewing gum: a double-blind trial in Thailand. <i>Clin Ther</i> 1988;10(2):183-6.
Batra (2005) <sup>100</sup>	Batra A, Klingler K, Landfeldt B, Friederich HM, Westin A, Danielsson T. Smoking reduction treatment with 4-mg nicotine gum: a double-blind, randomized, placebo-controlled study. <i>Clin Pharmacol Ther</i> 2005;78(6):689-96.
Blondal (1989) <sup>101</sup>	Blondal T. Controlled trial of nicotine polacrilex gum with supportive measures. <i>Arch Intern Med</i> 1989;149(8):1818-21.
Clavel-Chapelon (1997) <sup>102</sup>	Clavel-Chapelon F, Paoletti C, Benhamou S. Smoking cessation rates 4 years after treatment by nicotine gum and acupuncture. <i>Prev Med</i> 1997;26(1):25-8.
Cooper (2005) <sup>82</sup>	Cooper TV, Klesges RC, Debon MW, Zbikowski SM, Johnson KC, Clemens LH. A placebo controlled randomized trial of the effects of phenylpropanolamine and nicotine gum on cessation rates and postcessation weight gain in women. <i>Addict Behav</i> 2005;30(1):61-75.
Fagerström (1982) <sup>95</sup>	Fagerström KO. A comparison of psychological and pharmacological treatment in smoking cessation. <i>J Behav Med</i> 1982;5(3):343-51.
Fortmann (1988) <sup>83</sup>	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. <i>JAMA</i> 1988;260(11):1575-80.
Garvey (2000) <sup>84</sup>	Garvey AJ, Kinnunen T, Nordstrom BL, Utman CH, Doherty K, Rosner B, et al. Effects of nicotine gum dose by level of nicotine dependence. <i>Nicotine Tob Res</i> 2000;2(1):53-63.
Hall (1987) <sup>85</sup> <b>II</b>	Hall SM, Tunstall CD, Ginsberg D, Benowitz NL, Jones RT. Nicotine gum and behavioral treatment: a placebo controlled trial. <i>J Consult Clin Psychol</i> 1987;55(4):603-5.
Hall (1996) <sup>86</sup> (Depression)	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. <i>J Consult Clin Psychol</i> 1996;64(5):1003-9.
Herrera (1995) <sup>103</sup>	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. <i>Chest</i> 1995;108(2):447-51.
Hjalmarson (1984) <sup>96</sup> (CVD)	Hjalmarson AI. Effect of nicotine chewing gum in smoking cessation. A randomized, placebo-controlled, double-blind study. <i>JAMA</i> 1984;252(20):2835-8.
Hughes (1989) <sup>87</sup>	Hughes JR, Gust SW, Keenan RM, Fenwick JW, Healey ML. Nicotine vs placebo gum in general medical practice. <i>JAMA</i> 1989;261(9):1300-5.
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Jarvis (1982) <sup>93</sup>	Jarvis MJ, Raw M, Russell MA, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. <i>Br Med J (Clin Res Ed)</i> 1982;285(6341):537-40.
Kinnunen (2008) <sup>88</sup>	Kinnunen T, Korhonen T, Garvey AJ. Role of nicotine gum and pretreatment depressive symptoms in smoking cessation: twelve-month results of a randomized

<b>First author</b>	<b>Reference</b>
(Depression)	placebo controlled trial. <i>Int J Psychiatry Med</i> 2008;38(3):373-89.
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Oncken (2008) <sup>89</sup> (Pregnant)	Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Feinn R, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. <i>Obstet Gynecol</i> 2008;112(4):859-67.
Schneider (1983) <sup>90</sup>	Schneider NG, Jarvik ME, Forsythe AB, Read LL, Elliott ML, Schweiger A. Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. <i>Addict Behav</i> 1983;8(3):253-61.
Shiffman (2009) <sup>91</sup>	Shiffman S, Ferguson SG, Strahs KR. Quitting by gradual smoking reduction using nicotine gum: a randomized controlled trial. <i>Am J Prev Med</i> 2009;36(2):96-104.
Tonnesen (1988) <sup>98</sup>	Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnarsen AB, Forchammer H, et al. Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. <i>N Engl J Med</i> 1988;318(1):15-8.
Wennike (2003) <sup>97</sup>	Wennike P, Danielsson T, Landfeldt B, Westin Å, Tønnesen P. Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. <i>Addiction</i> 2003;98(10 4):1395-402.
<b>Nicotine lozenge versus placebo (1)</b>	
Shiffman (2002) <sup>104</sup>	Shiffman S, Dresler CM, Hajek P, Gilbert SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. <i>Arch Intern Med</i> 2002;162(11):1267-76.
<b>Nicotine sublingual tablet versus placebo (3)</b>	
Glover (2002) <sup>105</sup>	Glover ED, Glover PN, Franzon M, Sullivan CR, Cerullo CC, Howell RM, et al. A comparison of a nicotine sublingual tablet and placebo for smoking cessation. <i>Nicotine Tob Res</i> 2002;4(4):441-50.
Tonnesen (2006) <sup>106</sup> (COPD)	Tonnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. <i>Chest</i> 2006;130(2):334-42.
Wallstrom (2000) <sup>107</sup>	Wallstrom M, Nilsson F, Hirsch JM. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. <i>Addiction</i> 2000;95(8):1161-71.
<b>Nicotine oral inhaler versus placebo (5)</b>	
Bolliger (2000) <sup>108</sup>	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. <i>BMJ</i> 2000;321(7257):329-33.
Hjalmarson (1997) <sup>109</sup>	Hjalmarson A, Nilsson F, Sjoström L, Wiklund O. The nicotine inhaler in smoking cessation. <i>Arch Intern Med</i> 1997;157(15):1721-8.
Rennard (2006) <sup>110</sup>	Rennard SI, Glover ED, Leischow S, Daughton DM, Glover PN, Muramoto M, et al. Efficacy of the nicotine inhaler in smoking reduction: a double-blind, randomized trial. <i>Nicotine Tob Res</i> 2006;8(4):555-64.
Schneider (1996) <sup>111</sup>	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. <i>Addiction</i> 1996;91(9):1293-306.
Tonnesen (1993) <sup>112</sup>	Tonnesen P, Norregaard J, Mikkelsen K, Jorgensen S, Nilsson F. A double-blind trial of a nicotine inhaler for smoking cessation. <i>JAMA</i> 1993;269(10):1268-71.
<b>Nicotine nasal spray versus placebo (4)</b>	
Blondal (1997) <sup>113</sup>	Blondal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. <i>Eur Respir J</i> 1997;10(7):1585-90.
Hjalmarson	Hjalmarson A, Franzon M, Westin A, Wiklund O. Effect of nicotine nasal spray on

First author	Reference
(1994) <sup>114</sup>	smoking cessation. A randomized, placebo-controlled, double-blind study. <i>Arch Intern Med</i> 1994;154(22):2567-72.
Schneider (1995) <sup>115</sup>	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. <i>Addiction</i> 1995;90(12):1671-82.
Sutherland (1992) <sup>116</sup>	Sutherland G, Stapleton JA, Russell MA, Jarvis MJ, Hajek P, Belcher M, et al. Randomised controlled trial of nasal nicotine spray in smoking cessation. <i>Lancet</i> 1992;340(8815):324-9.

### C. NRT versus NRT ± behavioural supports

First author	Reference
<b>Patch versus nasal spray (2)</b>	
Croghan (2003) <sup>117</sup>	Croghan GA, Sloan JA, Croghan IT, Novotny P, Hurt RD, DeKrey WL, et al. Comparison of nicotine patch alone versus nicotine nasal spray alone versus a combination for treating smokers: a minimal intervention, randomized multicenter trial in a nonspecialized setting. <i>Nicotine Tob Res</i> 2003;5(2):181-7.
Lerman (2004) <sup>118</sup>	Lerman C, Kaufmann V, Rukstalis M, Patterson F, Perkins K, Audrain-McGovern J, et al. Individualizing nicotine replacement therapy for the treatment of tobacco dependence: a randomized trial. <i>Ann Intern Med</i> 2004;140(6):426-33.
<b>Patch versus gum versus placebo (1)</b>	
Moolchan (2005) <sup>119</sup> (Adolescent)	Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, et al. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. <i>Pediatrics</i> 2005;115(4):e407-e414.
<b>Lozenge versus gum (1)</b>	
Pack (2008) <sup>120</sup>	Pack QR, Jorenby DE, Fiore MC, Jackson T, Weston P, Piper ME, et al. A comparison of the nicotine lozenge and nicotine gum: an effectiveness randomized controlled trial. <i>WMJ</i> 2008;107(5):237-43.
<b>Patch versus inhaler (1)</b>	
Tønnesen (2000) <sup>121</sup> (lung problem)	Tønnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. <i>Eur Respir J</i> 2000;16(4):717-22.
<b>Spray versus gum versus inhaler (1)</b>	
Bolliger (2007) <sup>122</sup>	Bolliger CT, van Biljon X, Axelsson A. A nicotine mouth spray for smoking cessation: a pilot study of preference, safety and efficacy. <i>Respiration</i> 2007;74(2):196-201.
<b>Patch versus patch + behaviour (counselling or telephone) (8)</b>	
Alterman (2001) <sup>123</sup>	Alterman AI, Gariti P, Mulvaney F. Short- and long-term smoking cessation for three levels of intensity of behavioral treatment. <i>Psychol Addict Behav</i> 2001;15(3):261-4.
Bock (2008) <sup>124</sup> (Chest pain)	Bock BC, Becker BM, Niaura RS, Partridge R, Fava JL, Trask P. Smoking cessation among patients in an emergency chest pain observation unit: outcomes of the Chest Pain Smoking Study (CPSS). <i>Nicotine Tob Res</i> 2008;10(10):1523-31.
Lando (1997) <sup>125</sup>	Lando HA, Rolnick S, Klevan D, Roski J, Cherney L, Lauger G. Telephone support as an adjunct to transdermal nicotine in smoking cessation. <i>Am J Public Health</i> 1997;87(10):1670-4.
Lifrak (1997) <sup>126</sup>	Lifrak P, Gariti P, Alterman AI, McKay J, Volpicelli J, Sparkman T, et al. Results of two levels of adjunctive treatment used with the nicotine patch. <i>Am J Addict</i> 1997;6(2):93-8.

First author	Reference
Simon (2003) <sup>127</sup> (Hospitalized)	Simon JA, Carmody TP, Hudes ES, Snyder E, Murray J. Intensive smoking cessation counseling versus minimal counseling among hospitalized smokers treated with transdermal nicotine replacement: a randomized trial. <i>Am J Med</i> 2003;114(7):555-62.
Solomon (2000) <sup>128</sup> (Low-income)	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. <i>Prev Med</i> 2000;31(1):68-74.
Stein (2006) <sup>129</sup> (Methadone)	Stein MD, Weinstock MC, Herman DS, Anderson BJ, Anthony JL, Niaura R. A smoking cessation intervention for the methadone-maintained. <i>Addiction</i> 2006;101(4):599-607.
Wiggers (2006) <sup>130</sup> (CVD)	Wiggers LC, Smets EM, Oort FJ, Peters RJ, Storm-Versloot MN, Vermeulen H, et al. The effect of a minimal intervention strategy in addition to nicotine replacement therapy to support smoking cessation in cardiovascular outpatients: a randomized clinical trial. <i>Eur J Cardiovasc Prev Rehabil</i> 2006;13(6):931-7.
<b>Gum versus gum + behaviour (5)</b>	
Fortmann (1995) <sup>131</sup>	Fortmann SP, Killen JD. Nicotine gum and self-help behavioral treatment for smoking relapse prevention: results from a trial using population-based recruitment. <i>J Consult Clin Psychol</i> 1995;63(3):460-8.
Ginsberg (1992) <sup>132</sup>	Ginsberg D, Hall SM, Rosinski M. Partner support, psychological treatment, and nicotine gum in smoking treatment: an incremental study. <i>Int J Addict</i> 1992;27(5):503-14.
Hall (1985) <sup>133</sup>	Hall SM, Tunstall C, Rugg D, Jones RT, Benowitz N. Nicotine gum and behavioral treatment in smoking cessation. <i>J Consult Clin Psychol</i> 1985;53(2):256-8.
Hall (1987) <sup>85</sup> <b>II</b>	Hall SM, Tunstall CD, Ginsberg D, Benowitz NL, Jones RT. Nicotine gum and behavioral treatment: a placebo controlled trial. <i>J Consult Clin Psychol</i> 1987;55(4):603-5.
Killen (1984) <sup>134</sup>	Killen JD, Maccoby N, Taylor CB. Nicotine gum and self-regulation training in smoking relapse prevention. <i>Behav Ther</i> 1984;15(3):234-48.

#### D. NRT + behaviour versus control (usual care) (10)

First author	Reference
Baker (2006) <sup>135</sup> (Psychotic)	Baker A, Richmond R, Haile M, Lewin TJ, Carr VJ, Taylor RL, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. <i>Am J Psychiatry</i> 2006;163(11):1934-42.
Lacasse (2008) <sup>141</sup> (Hospitalized)	Lacasse Y, Lamontagne R, Martin S, Simard S, Arsenault M. Randomized trial of a smoking cessation intervention in hospitalized patients. <i>Nicotine Tob Res</i> 2008;10(7):1215-21.
Lewis (1998) <sup>66</sup> (Hospitalized) <b>II</b>	Lewis SF, Piasecki TM, Fiore MC, Anderson JE, Baker TB. Transdermal nicotine replacement for hospitalized patients: a randomized clinical trial. <i>Prev Med</i> 1998;27(2):296-303.
Mohiuddin (2007) <sup>138</sup> (Hospitalized)	Mohiuddin SM, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. <i>Chest</i> 2007;131(2):446-52.
Molyneux (2003) <sup>142</sup> (Hospitalized)	Molyneux A, Lewis S, Leivers U, Anderton A, Antoniak M, Brackenridge A, et al. Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. <i>Thorax</i> 2003;58(6):484-8.
Nagle (2005) <sup>136</sup> (Hospitalized)	Nagle AL, Hensley MJ, Schofield MJ, Koschel AJ. A randomised controlled trial to evaluate the efficacy of a nurse-provided intervention for hospitalised smokers. <i>Aust</i>

First author	Reference
	<i>N Z J Public Health</i> 2005;29(3):285-91.
Reid (2008) <sup>139</sup> (Substance abuse)	Reid MS, Fallon B, Sonne S, Flammino F, Nunes EV, Jiang H, et al. Smoking cessation treatment in community-based substance abuse rehabilitation programs. <i>J Subst Abuse Treat</i> 2008;35(1):68-77.
Rodríguez-Artalejo (2003) <sup>143</sup>	Rodríguez-Artalejo F, Lafuente UP, Guallar-Castillón P, Garteizurrekoa DP, Sáinz MO, Díez Azcárate JI, et al. One year effectiveness of an individualised smoking cessation intervention at the workplace: a randomised controlled trial. <i>Occup Environ Med</i> 2003;60(5):358-63.
Simon (1997) <sup>140</sup> (Surgery)	Simon JA, Solkowitz SN, Carmody TP, Browner WS. Smoking cessation after surgery. A randomized trial. <i>Arch Intern Med</i> 1997;157(12):1371-6.
Wakefield (2004) <sup>137</sup> (Cancer)	Wakefield M, Olver I, Whitford H, Rosenfeld E. Motivational interviewing as a smoking cessation intervention for patients with cancer: randomized controlled trial. <i>Nurs Res</i> 2004;53(6):396-405.

### E. NRT + behaviour (counselling) versus behaviour (counselling) (14)

First author	Reference
Cinciripini (1996) <sup>145</sup>	Cinciripini PM, Cinciripini LG, Wallfisch A, Haque W, Van Vunakis H. Behavior therapy and the transdermal nicotine patch: effects on cessation outcome, affect, and coping. <i>J Consult Clin Psychol</i> 1996;64(2):314-23.
Gilbert (1989) <sup>154</sup>	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. <i>J Fam Pract</i> 1989;28(1):49-55.
Hand (2002) <sup>155</sup> (Hospitalized)	Hand S, Edwards S, Campbell IA, Cannings R. Controlled trial of three weeks nicotine replacement treatment in hospital patients also given advice and support. <i>Thorax</i> 2002;57(8):715-8.
Harackiewicz (1988) <sup>146</sup>	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. <i>Addict Behav</i> 1988;13(4):319-30.
Hill (1993) <sup>147</sup>	Hill RD, Rigdon M, Johnson S. Behavioral smoking cessation treatment for older chronic smokers. <i>Behav Ther</i> 1993;24(2):321-9.
Martin (1997) <sup>148</sup> (Alcohol)	Martin JE, Calfas KJ, Patten CA, Polarek M, Hofstetter CR, Noto J, et al. Prospective evaluation of three smoking interventions in 205 recovering alcoholics: one-year results of Project SCRAP-Tobacco. <i>J Consult Clin Psychol</i> 1997;65(1):190-4.
Molyneux (2003) <sup>142</sup> (Hospitalized) <b>II</b>	Molyneux A, Lewis S, Leivers U, Anderton A, Antoniak M, Brackenridge A, et al. Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. <i>Thorax</i> 2003;58(6):484-8.
Niaura (1994) <sup>149</sup>	Niaura R, Goldstein MG, Abrams DB. Matching high- and low-dependence smokers to self-help treatment with or without nicotine replacement. <i>Prev Med</i> 1994;23(1):70-7.
Niaura (1999) <sup>150</sup>	Niaura R, Abrams DB, Shadel WG, Rohsenow DJ, Monti PM, Sirota AD. Cue exposure treatment for smoking relapse prevention: a controlled clinical trial. <i>Addiction</i> 1999;94(5):685-95.
Okuyemi (2007) <sup>151</sup>	Okuyemi KS, James AS, Mayo MS, Nollen N, Catley D, Choi WS, et al. Pathways to health: a cluster randomized trial of nicotine gum and motivational interviewing

First author	Reference
(Low-income)	for smoking cessation in low-income housing. <i>Health Educ Behav</i> 2007;34(1):43-54.
Pirie (1992) <sup>152</sup>	Pirie PL, McBride CM, Hellerstedt W, Jeffery RW, Hatsukami D, Allen S, et al. Smoking cessation in women concerned about weight. <i>Am J Public Health</i> 1992;82(9):1238-43.
Pollak (2007) <sup>153</sup> (Pregnant)	Pollak KI, Oncken CA, Lipkus IM, Lyna P, Swamy GK, Pletsch PK, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. <i>Am J Prev Med</i> 2007;33(4):297-305.
Richmond (1993) <sup>156</sup>	Richmond RL, Makinson RJ, Kehoe LA, Giugni AA, Webster IW. One-year evaluation of three smoking cessation interventions administered by general practitioners. <i>Addict Behav</i> 1993;18(2):187-99.
Segnan (1991) <sup>157</sup>	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. <i>Cancer Causes Control</i> 1991;2(4):239-46.

## F. Bupropion

First author	Reference
<b>Bupropion versus placebo (23)</b>	
Ahluwalia (2002) <sup>158</sup>	Ahluwalia JS, Harris KJ, Catley D, Okuyemi KS, Mayo MS. Sustained-release bupropion for smoking cessation in African Americans: a randomized controlled trial. <i>JAMA</i> 2002;288(4):468-74.
Aubin (2004) <sup>173</sup>	Aubin HJ, Lebargy F, Berlin I, Bidaut-Mazel C, Chemali-Hudry J, Lagrue G. Efficacy of bupropion and predictors of successful outcome in a sample of French smokers: a randomized placebo-controlled trial. <i>Addiction</i> 2004;99(9):1206-18.
Brown (2007) <sup>159</sup>	Brown RA, Niaura R, Lloyd-Richardson EE, Strong DR, Kahler CW, Abrantes AM, et al. Bupropion and cognitive-behavioral treatment for depression in smoking cessation. <i>Nicotine Tob Res</i> 2007;9(7):721-30.
Evins (2001, 2004) <sup>160,181</sup> (Schizo)	Evins AE, Mays VK, Rigotti NA, Tisdale T, Cather C, Goff DC. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. <i>Nicotine Tob Res</i> 2001;3(4):397-403.  Evins AE, Cather C, Rigotti NA, Freudenreich O, Henderson DC, Olm-Shipman CM, et al. Two-year follow-up of a smoking cessation trial in patients with schizophrenia: increased rates of smoking cessation and reduction. <i>J Clin Psychiatry</i> 2004;65(3):307-11.
Evins (2005) <sup>161</sup> (Schizo)	Evins AE, Cather C, Deckersbach T, Freudenreich O, Culhane MA, Olm-Shipman CM, et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. <i>J Clin Psychopharmacol</i> 2005;25(3):218-25.
Fossati (2007) <sup>174</sup>	Fossati R, Apolone G, Negri E, Compagnoni A, La VC, Mangano S, et al. A double-blind, placebo-controlled, randomized trial of bupropion for smoking cessation in primary care. <i>Arch Intern Med</i> 2007;167(16):1791-7.
George (2002) <sup>162</sup> (Schizo)	George TP, Vessicchio JC, Termine A, Bregartner TA, Feingold A, Rounsaville BJ, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. <i>Biol Psychiatry</i> 2002;52(1):53-61.
Gonzales (2001) <sup>163</sup>	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. <i>Clin Pharmacol Ther</i> 2001;69(6):438-44.
Haggström	Haggström FM, Chatkin JM, Sussenbach-Vaz E, Cesari DH, Fam CF, Fritscher CC. A

First author	Reference
(2006) <sup>175</sup>	controlled trial of nortriptyline, sustained-release bupropion and placebo for smoking cessation: preliminary results. <i>Pulm Pharmacol Ther</i> 2006;19(3):205-9.
Hall (2002) <sup>164</sup>	Hall SM, Humfleet GL, Reus VI, Muñoz RF, Hartz DT, Maude-Griffin R. Psychological intervention and antidepressant treatment in smoking cessation. <i>Arch Gen Psychiatry</i> 2002;59(10):930-6.
Hatsukami (2004) <sup>165</sup>	Hatsukami DK, Rennard S, Patel MK, Kotlyar M, Malcolm R, Nides MA, et al. Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking. <i>Am J Med</i> 2004;116(3):151-7.
Hertzberg (2001) <sup>166</sup> (Stress)	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. <i>J Clin Psychopharmacol</i> 2001;21(1):94-8.
Holt (2005) <sup>176</sup>	Holt S, Timu-Parata C, Ryder-Lewis S, Weatherall M, Beasley R. Efficacy of bupropion in the indigenous Maori population in New Zealand. <i>Thorax</i> 2005;60(2):120-3.
Hurt (1997) <sup>167</sup>	Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. <i>N Engl J Med</i> 1997;337(17):1195-202.
McCarthy (2008) <sup>168</sup> <b>II</b>	McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Fiore MC, et al. A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. <i>Nicotine Tob Res</i> 2008;10(4):717-29.
Muramoto (2007) <sup>169</sup> (Adolescents)	Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. <i>Arch Pediatr Adolesc Med</i> 2007;161(11):1068-74.
Rigotti (2006) <sup>170</sup> (hospitalized)	Rigotti NA, Thorndike AN, Regan S, McKool K, Pasternak RC, Chang Y, et al. Bupropion for smokers hospitalized with acute cardiovascular disease. <i>Am J Med</i> 2006;119(12):1080-7.
Simon (2009) <sup>172</sup>	Simon JA, Duncan C, Huggins J, Solkowitz S, Carmody TP. Sustained-release bupropion for hospital-based smoking cessation: a randomized trial. <i>Nicotine Tob Res</i> 2009;11(6):663-9.
Tashkin (2001) <sup>171</sup> (COPD)	Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. <i>Lancet</i> 2001;357(9268):1571-5.
Tønnesen (2003) <sup>178</sup>	Tønnesen P, Tonstad S, Hjalmarson A, Leborgy F, Van Spiegel PI, Hider A, et al. A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. <i>J Intern Med</i> 2003;254(2):184-92.
Tonstad (2003) <sup>179</sup> (CVD)	Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. <i>Eur Heart J</i> 2003;24(10):946-55.
Wagena (2005) <sup>177</sup> (COPD)	Wagena EJ, Knipschild PG, Huibers MJ, Wouters EF, van Schayck CP. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. <i>Arch Intern Med</i> 2005;165(19):2286-92.
Zellweger (2005) <sup>180</sup>	Zellweger JP, Boelcskei PL, Carrozzi L, Sepper R, Sweet R, Hider AZ. Bupropion SR vs placebo for smoking cessation in health care professionals. <i>Am J Health Behav</i> 2005;29(3):240-9.
<b>Bupropion versus patch (1)</b>	
Uyar (2007) <sup>182</sup>	Uyar M, Filiz A, Bayram N, Elbek O, Herken H, Topcu A, et al. A randomized trial of smoking cessation. Medication versus motivation. <i>Saudi Med J</i> 2007;28(6):922-6.
<b>Bupropion versus bupropion + counselling (1)</b>	
McCarthy	McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Fiore MC, et al.

First author	Reference
(2008) <sup>168</sup> <b>II</b>	A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. <i>Nicotine Tob Res</i> 2008;10(4):717-29.

## G. Combined therapy (10)

First author	Reference
<b>Patch + spray versus oatch + placebo spray (1)</b>	
Blondal (1999) <sup>183</sup>	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. <i>BMJ</i> 1999;318(7179):285-8.
<b>Inhaler + patch versus inhaler + placebo patch (1)</b>	
Bohadana (2000, 2003) <sup>184,364</sup>	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. <i>Arch Intern Med</i> 2000;160(20):3128-34.  Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Gender differences in quit rates following smoking cessation with combination nicotine therapy: influence of baseline smoking behavior. <i>Nicotine Tob Res</i> 2003;5(1):111-6.
<b>Bupropion + gum versus bupropion + placebo gum (1)</b>	
Piper (2007) <sup>187</sup>	Piper ME, Federman EB, McCarthy DE, Bolt DM, Smith SS, Fiore MC, et al. Efficacy of bupropion alone and in combination with nicotine gum. <i>Nicotine Tob Res</i> 2007;9(9):947-54.
<b>NRT + bupropion versus NRT + placebo bupropion (4)</b>	
Evins (2007) <sup>191</sup> (Schizo)	Evins AE, Cather C, Culhane MA, Birnbaum A, Horowitz J, Hsieh E, et al. A 12-week double-blind, placebo-controlled study of bupropion SR added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. <i>J Clin Psychopharmacol</i> 2007;27(4):380-6.
George (2008) <sup>190</sup> (Schizo)	George TP, Vessicchio JC, Sacco KA, Weinberger AH, Dudas MM, Allen TM, et al. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. <i>Biol Psychiatry</i> 2008;63(11):1092-6.
Killen (2004) <sup>192</sup> (Adolescents)	Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, Stone C, et al. Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. <i>J Consult Clin Psychol</i> 2004;72(4):729-35.
Simon (2004) <sup>193</sup>	Simon JA, Duncan C, Carmody TP, Hudes ES. Bupropion for smoking cessation: a randomized trial. <i>Arch Intern Med</i> 2004;164(16):1797-803.
<b>Bupropion + patch versus bupropion versus patch versus placebo (or control) (1)</b>	
Jorenby (1999), <sup>188</sup> Smith (2003) <sup>197</sup>	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. <i>N Engl J Med</i> 1999;340(9):685-91.  Smith SS, Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, et al. Targeting smokers at increased risk for relapse: treating women and those with a history of depression. <i>Nicotine Tob Res</i> 2003;5(1):99-109.
<b>Patch + gum versus patch + placebo gum (2)</b>	
Kornitzer (1995) <sup>185</sup>	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. <i>Prev Med</i> 1995;24(1):41-7.
Cooney (2009) <sup>186</sup>	Cooney NL, Cooney JL, Perry BL, Carbone M, Cohen EH, Steinberg HR, et al. Smoking cessation during alcohol treatment: a randomized trial of combination nicotine patch plus nicotine gum. <i>Addiction</i> 2009;104(9):1588-96.

First author	Reference
<b>Patch versus patch + inhaler + bupropion (1)</b>	
Steinberg (2009) <sup>189</sup> (medically ill)	Steinberg MB, Greenhaus S, Schmelzer AC, Bover MT, Foulds J, Hoover DR, et al. Triple-combination pharmacotherapy for medically ill smokers: a randomized trial. <i>Ann Intern Med</i> 2009;150(7):447-54.

#### Appendix 4b: For question 3

First author	Reference
<b>Pay versus free nicotine patch</b>	
Hays (1999) <sup>62</sup> <b>II</b>	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. <i>Am J Public Health</i> 1999;89(11):1701-7.
Kaper (2005) <sup>195</sup>	Kaper J, Wagena EJ, Willemsen MC, van Schayck CP. Reimbursement for smoking cessation treatment may double the abstinence rate: results of a randomized trial. <i>Addiction</i> 2005;100(7):1012-20.
<b>Incentive versus control</b>	
Volpp (2009) <sup>194</sup>	Volpp KG, Troxel AB, Pauly MV, Glick HA, Puig A, Asch DA, et al. A randomized, controlled trial of financial incentives for smoking cessation. <i>N Engl J Med</i> 2009;360(7):699-709.

#### Appendix 4c: For question 11

First author	Reference
Alberg (2004) <sup>279</sup>	Alberg AJ, Stashefsky MR, Burke A, Rasch KA, Stewart N, Kline JA, et al. The influence of offering free transdermal nicotine patches on quit rates in a local health department's smoking cessation program. <i>Addict Behav</i> 2004;29(9):1763-78.
An (2006) <sup>280</sup>	An LC, Schillo BA, Kavanaugh AM, Lachter RB, Luxenberg MG, Wendling AH, et al. Increased reach and effectiveness of a statewide tobacco quitline after the addition of access to free nicotine replacement therapy. <i>Tob Control</i> 2006;15:286-93.
Busch (2004) <sup>365</sup>	Busch S, Falba T, Duchovny N, Jofre-Bonet M, O'Malley S, Sindelar J. Value to smokers of improved cessation products: evidence from a willingness-to-pay survey. <i>Nicotine Tob Res</i> 2004;6(4):631-9.
Bush (2008) <sup>366</sup>	Bush TM, McAfee T, Deprey M, Mahoney L, Fellows JL, McClure J, et al. The impact of a free nicotine patch starter kit on quit rates in a state quit line. <i>Nicotine Tob Res</i> 2008;10(9):1511-6.
Cox (1990) <sup>284</sup>	Cox JL, McKenna JP. Nicotine gum: does providing it free in a smoking cessation program alter success rates? <i>J Fam Pract</i> 1990;31(3):278-80.
Cummings (2006) <sup>281</sup>	Cummings KM, Hyland A, Fix B, Bauer U, Celestino P, Carlin-Menter S, et al. Free nicotine patch giveaway program. 12-month follow-up of participants. <i>Am J Prev Med</i> 2006;31(2):181-4.
Cunningham (2008) <sup>286</sup>	Cunningham JA, Selby PL. Intentions of smokers to use free nicotine replacement therapy. <i>CMAJ</i> 2008;179(2):145-6.
Curry (1998) <sup>288</sup>	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. <i>N Engl J Med</i> 1998;339(10):673-9.
Halpin (2007) <sup>287</sup>	Halpin HA, McMenamin SB, Shade SB. The demand for health insurance coverage for tobacco dependence treatments: support for a benefit mandate and willingness to pay. <i>Nicotine Tob Res</i> 2007;9(12):1269-76.

First author	Reference
Miller (2005) <sup>283</sup>	Miller N, Frieden TR, Liu SY, Matte TD, Mostashari F, Deitcher DR, et al. Effectiveness of a large-scale distribution programme of free nicotine patches: a prospective evaluation. <i>Lancet</i> 2005;365(9474):1849-54.
Petersen (2006) <sup>289</sup>	Petersen R, Garrett JM, Melvin CL, Hartmann KE. Medicaid reimbursement for prenatal smoking intervention influences quitting and cessation. <i>Tob Control</i> 2006;15(1):30-4.
Tinkelman (2007) <sup>282</sup>	Tinkelman D, Wilson SM, Willett J, Sweeney CT. Offering free NRT through a tobacco quitline: impact on utilisation and quit rates. <i>Tob Control</i> 2007;16 Suppl 1:i42-i46.
West (2005) <sup>285</sup>	West R, DiMarino ME, Gitchell J, McNeill A. Impact of UK policy initiatives on use of medicines to aid smoking cessation. <i>Tob Control</i> 2005;14(3):166-71.

#### Appendix 4d: For question 12

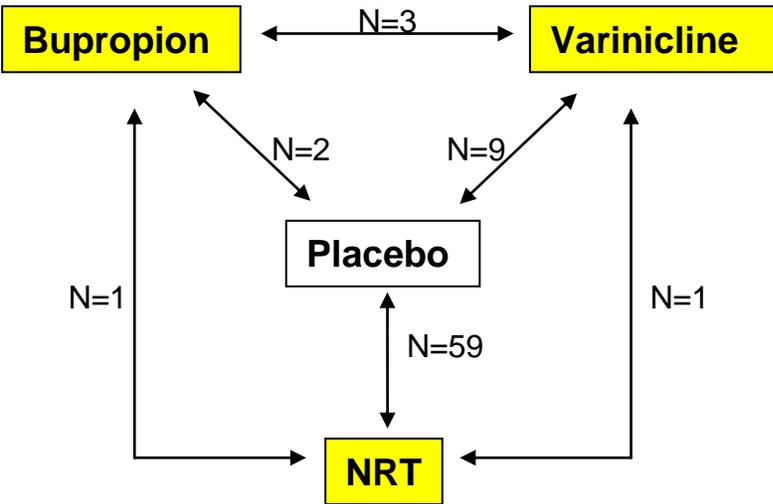
First author	Reference
<b>A. Equitable access –specific populations, accessibility issues, barriers</b>	
Doolan (2008) <sup>295</sup>	Doolan DM, Froelicher ES. Smoking cessation interventions and older adults. <i>Prog Cardiovasc Nurs</i> 2008;23(3):119-27.
Edmonds (2007) <sup>297</sup>	Edmonds N, Bremner J. Improving access to stop smoking support for people with mental health problems. <i>Journal of Public Mental Health</i> 2007;6(1):10-9.
Fernández (2006) <sup>367</sup>	Fernández E, Schiaffino A, Borrell C, Benach J, Ariza C, Ramon JM, et al. Social class, education, and smoking cessation: long-term follow-up of patients treated at a smoking cessation unit. <i>Nicotine Tob Res</i> 2006;8(1):29-36.
Fu (2005) <sup>368</sup>	Fu SS, Sherman SE, Yano EM, van Ryn M, Lanto AB, Joseph AM. Ethnic disparities in the use of nicotine replacement therapy for smoking cessation in an equal access health care system. <i>Am J Health Promot</i> 2005;20(2):108-16.
Gollust (2008) <sup>291</sup>	Gollust SE, Schroeder SA, Warner KE. Helping smokers quit: understanding the barriers to utilization of smoking cessation services. <i>Milbank Q</i> 2008;86(4):601-27.
Hall (2007) <sup>296</sup>	Hall SM. Nicotine interventions with comorbid populations. <i>Am J Prev Med</i> 2007;33(6 Suppl):S406-S413.
Hammond (2004) <sup>292</sup>	Hammond D, McDonald PW, Fong GT, Borland R. Do smokers know how to quit? Knowledge and perceived effectiveness of cessation assistance as predictors of cessation behaviour. <i>Addiction</i> 2004;99(8):1042-8.
Henningfield (2000) <sup>306</sup>	Henningfield JE, Michaelides T, Sussman S. Developing treatment for tobacco addicted youth -- issues and challenges. <i>J Child Adolesc Subst Abuse</i> 2000;9(4):5-26.
Ivers (2004) <sup>302</sup>	Ivers RG. An evidence-based approach to planning tobacco interventions for Aboriginal people. <i>Drug Alcohol Rev</i> 2004;23(1):5-9.
Leatherdale (2007) <sup>369</sup>	Leatherdale ST, McDonald PW. Youth smokers' beliefs about different cessation approaches: Are we providing cessation interventions they never intend to use? <i>Cancer Causes Control</i> 2007;18(7):783-91.
Lillard (2007) <sup>370</sup>	Lillard DR, Plassmann V, Kenkel D, Mathios A. Who kicks the habit and how they do it: socioeconomic differences across methods of quitting smoking in the USA. <i>Soc Sci Med</i> 2007;64(12):2504-19.
Macdonald (2007) <sup>307</sup>	Macdonald S, Rothwell H, Moore L. Getting it right: designing adolescent-centred smoking cessation services. <i>Addiction</i> 2007;102(7):1147-50.
McEwen (2009) <sup>294</sup>	McEwen A, West R. Do implementation issues influence the effectiveness of medications? The case of nicotine replacement therapy and bupropion in UK Stop Smoking Services. <i>BMC Public Health</i> 2009;9:28.
NICE	<i>Reducing the rate of premature deaths from cardiovascular disease and other</i>

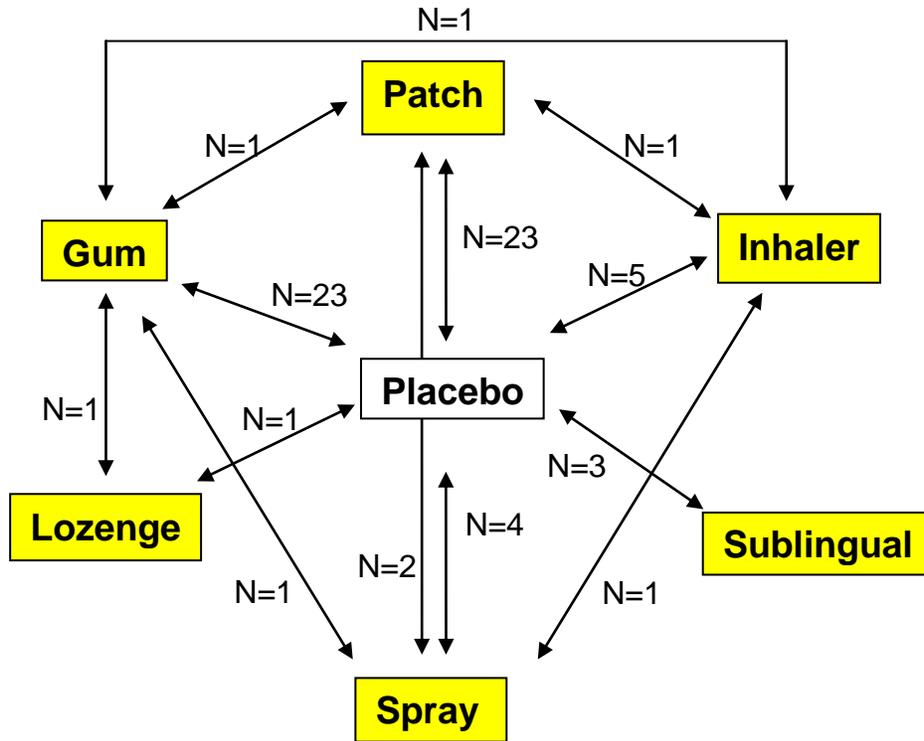
First author	Reference
(2008) <sup>371</sup>	<i>smoking-related diseases: finding and supporting those most at risk and improving access to services.</i> [NICE public health guidance 15]. London: National Institute for Health and Clinical Excellence; 2008 Sep.
Okuyemi (2006) <sup>301</sup>	Okuyemi KS, Caldwell AR, Thomas JL, Born W, Richter KP, Nollen N, et al. Homelessness and smoking cessation: insights from focus groups. <i>Nicotine Tob Res</i> 2006;8(2):287-96.
Pletsch (2003) <sup>299</sup>	Pletsch PK, Morgan S, Pieper AF. Context and beliefs about smoking and smoking cessation. <i>MCN Am J Matern Child Nurs</i> 2003;28(5):320-5.
Prokhorov (2006) <sup>308</sup>	Prokhorov AV, Winickoff JP, Ahluwalia JS, Ossip-Klein D, Tanski S, Lando HA, et al. Youth tobacco use: a global perspective for child health care clinicians. <i>Pediatrics</i> 2006;118(3):e890-e903.
Roddy (2006) <sup>300</sup>	Roddy E, Antoniak M, Britton J, Molyneux A, Lewis S. Barriers and motivators to gaining access to smoking cessation services amongst deprived smokers -- a qualitative study. <i>BMC Health Serv Res</i> 2006;6:147.
Thomas (2008) <sup>372</sup>	Thomas S, Fayter D, Misso K, Ogilvie D, Petticrew M, Sowden A, et al. Population tobacco control interventions and their effects on social inequalities in smoking: systematic review. <i>Tob Control</i> 2008;17(4):230-7.
Wardman (2004) <sup>303</sup>	Wardman AED, Khan NA. Tobacco cessation pharmacotherapy use among First Nations persons residing within British Columbia. <i>Nicotine Tob Res</i> 2004;6(4):689-92.
<b>B. Equitable access –frameworks, programs</b>	
Bauld (2005) <sup>373</sup>	Bauld L, Coleman T, Adams C, Pound E, Ferguson J. Delivering the English smoking treatment services. <i>Addiction</i> 2005;100(Suppl 2):19-27.
Carver (2003) <sup>374</sup>	Carver V, Reinert B, Range LM, Campbell C, Boyd N. Nonprofit organizations versus government agencies to reduce tobacco use. <i>J Public Health Policy</i> 2003;24(2):181-94.
Edwards (1999) <sup>313</sup>	Edwards R, Brown JS, Hodgson P, Kyle D, Reed D, Wallace B. An action plan for tobacco control at regional level. <i>Public Health</i> 1999;113(4):165-70.
Fisher (2005) <sup>375</sup>	Fisher E, Musick J, Scott C, Miller JP, Gram R, Richardson V, et al. Improving clinic- and neighborhood-based smoking cessation services within federally qualified health centers serving low-income, minority neighborhoods. <i>Nicotine Tob Res</i> 2005;7 Suppl 1:S45-56.
Gulliver (2004) <sup>316</sup>	Gulliver SB, Wolfsdorf BA, Morissette SB. Treating tobacco dependence: development of a smoking cessation treatment program for outpatient mental health clinics. <i>Cognitive and Behavioral Practice</i> 2004;11(3):315-30.
Hamlett-Berry (2009) <sup>376</sup>	Hamlett-Berry K, Davison J, Kivlahan DR, Matthews MH, Hendrickson JE, Almenoff PL. Evidence-based national initiatives to address tobacco use as a public health priority in the Veterans Health Administration. <i>Mil Med</i> 2009;174(1):29-34.
Heath (2006) <sup>319</sup>	Heath J, Andrews J. Using evidence-based educational strategies to increase knowledge and skills in tobacco cessation. <i>Nurs Res</i> 2006;55(4 Suppl):S44-S50.
McNeill (2005) <sup>315</sup>	McNeill A, Raw M, Whybrow J, Bailey P. A national strategy for smoking cessation treatment in England. <i>Addiction</i> 2005;100(Suppl 2):1-11.
Mecklenburg (2003) <sup>311</sup>	Mecklenburg RE. Public health issues in treating tobacco use. <i>Am J Med Sci</i> 2003;326(4):255-61.
Orleans (2007) <sup>377</sup>	Orleans CT. Increasing the demand for and use of effective smoking-cessation treatments. Reaping the full health benefits of tobacco-control science and policy gains-in our lifetime. <i>Am J Prev Med</i> 2007;33(6 Suppl):S340-S348.
Pine (1999) <sup>378</sup>	Pine D, Sullivan S, Conn SA, David C. Promoting tobacco cessation in primary care practice. <i>Prim Care</i> 1999;26(3):591-610.

First author	Reference
Raw (2005) <sup>314</sup>	Raw M, McNeill A, Coleman T. Lessons from the English smoking treatment services. <i>Addiction</i> 2005;100(Suppl 2):84-91.
Reid (2006) <sup>379</sup>	Reid RD, Lipe AL, Quinlan B. Promoting smoking cessation during hospitalization for coronary artery disease. <i>Can J Cardiol</i> 2006;22(9):775-80.
<b>C. Accountability</b>	
Brewster (2007) <sup>318</sup>	Brewster JM, Victor JC, Ashley MJ. Views of Ontarians about health professionals' smoking cessation advice. <i>Can J Public Health</i> 2007;98(5):395-9.
Cornuz (2007) <sup>380</sup>	Cornuz J. Smoking cessation interventions in clinical practice. <i>Eur J Vasc Endovasc Surg</i> 2007;34(4):397-404.
Curry (2008) <sup>310</sup>	Curry SJ, Keller PA, Orleans CT, Fiore MC. The role of health care systems in increased tobacco cessation. <i>Annu Rev Public Health</i> 2008;29:411-28.
Davis (2000) <sup>309</sup>	Davis RM, Slade J, Ferry LH. Quality improvement and accountability in the treatment of tobacco dependence: the need for a national training and certification programme. <i>Tob Control</i> 2000;9(4):355-8.
Easton (2001) <sup>381</sup>	Easton A, Husten C, Elon L, Pederson L, Frank E. Non-primary care physicians and smoking cessation counseling: Women Physicians' Health Study. <i>Women Health</i> 2001;34(4):15-29.
Easton (2001) <sup>382</sup>	Easton A, Husten C, Malarcher A, Elon L, Caraballo R, Ahluwalia I, et al. Smoking cessation counseling by primary care women physicians: Women Physicians' Health Study. <i>Women Health</i> 2001;32(4):77-91.
Ibrahim (2004) <sup>312</sup>	Ibrahim JK, Tsoukalas TH, Glantz SA. Public health foundations and the tobacco industry: lessons from Minnesota. <i>Tob Control</i> 2004;13(3):228-36.

# APPENDIX 5: NETWORK DIAGRAMS CONNECTING PLACEBO-CONTROLLED AND HEAD-TO-HEAD TRIALS

The network diagrams shown below present of the numbers and types of studies available for MTC meta-analyses performed in the clinical review of this health technology assessment. The first figure represents the structure of the data for analyses where all nicotine replacement therapies were considered as one class, while the second figure represents the structure of the data available for comparisons amongst different types of NRT. The number of available studies may have been smaller for some analyses where some included studies failed to report relevant data.





## APPENDIX 6: CHARACTERISTICS OF THE INCLUDED TRIALS

### Appendix 6a: Study characteristics

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
<b>Varenicline vs. placebo</b>							
Nakamura (2007); <sup>47</sup> RCT, double-blind, parallel	To evaluate the efficacy and dose-response relationship of varenicline in Japanese smokers  Varenicline improved the abstinence rates in a dose-dependent manner during treatment and follow-up	Japan; multicentre (19 sites); Pfizer Inc.	12 wks; 52 wks	Varenicline vs. placebo	12 wks of treatment with varenicline (0.25, 0.5, or 1 mg BID) or placebo Dose titration during wk-1 All received educational booklet and brief smoking-cessation counselling (10 min at each clinic visit, starting at baseline until end of treatment) Target quit date (TQD) started at wk-1 Telephone contact at TQD + 3 days (with up to 5 min counselling) 40 wks non-treatment follow-up with 6 clinic visits (wks 13, 16, 24, 36, 44, and 52) 5 telephone contacts (wks 20, 28, 32, 40 and 48)	End-expiratory CO level $\leq 10$ ppm Continuous abstinence rate (CAR) – no reported smoking (not even a puff) or other nicotine use during the indicated period. 7-day point prevalence (pp)abstinence – reported abstinence during the past 7 days	Total: 618 / 577 (93.4%) / 510 (82.5%)
Niaura (2008); <sup>48</sup> RCT, double-	To determine whether self-regulated flexible	US; multicentre (5 sites); Pfizer Inc.	12 wks; 52 wks	Varenicline vs. placebo	Wk-1 titration: one tablet daily (0.5 mg/day or placebo) for 3 days, then	At each visit, participants provided self-	Total: 312 / 232 (74.4%) / 189

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
blind, parallel	dosing with varenicline tartrate is safe and effective for smoking cessation  Self-regulated, flexible dosing schedule of varenicline was efficacious at the end of treatment and follow-up				one tablet twice daily (1.0 mg/day or placebo) for 4 days. Flexible dosing: after wk-1, participants were allowed to modify their own dosage in response to AEs. They were instructed to take at least 1 tablet daily and not exceed two tablets BID through wk-12 All received educational booklet and weekly brief counselling (up to 10 min) TQD coincided with wk-1 clinical visit	reported abstinence during the past 7 days; CAR for wks 4-7, 9-12, 9-24 and 9-52; 7-day pp for wks 12, 24 and 52 Abstinence was verified by exhaled CO level $\leq 10$ ppm	(60.6%)
Oncken (2006); <sup>49</sup> RCT, double-blind, parallel	To study the efficacy and safety of varenicline for smoking cessation  Varenicline therapy at 0.5 mg and 1.0 mg twice daily was efficacious for smoking cessation	US; multicentre (10 sites); Pfizer	12 wks; 52 wks	Varenicline vs. placebo	Treatment: 5 arms: 1. 0.5 mg BID non-titrated for 12 wks 2. 0.5 mg BID titrated: 0.5 mg QD for 7 days, then 0.5 mg BID for 11 wks 3. 1.0 mg BID non-titrated for 12 wks 4. 1.0 mg BID titrated: 0.5 mg QD for 7 days, then 0.5 mg BID for 11 wks 5. Placebo All received booklet and	Self-reported abstinence verified by CO levels $\leq 10$ ppm CAR at wks 4-7, 9-12 and 9-52	639 / 398 (62.3%) / 309 (48.4%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					brief counselling (up to 10 min) on smoking cessation TQD: wk 1 visit (7 days later) Treatment phase: wks 1,2, 4, 7, and 12 Follow-up visits: wks 13, 24, and 52		
Tsai (2007); <sup>50</sup> RCT, double-blind, parallel	To evaluate the efficacy and tolerability of 1 mg BID varenicline for smoking cessation in smokers in Taiwan and Korea Varenicline was an efficacious and well-tolerated therapy for smoking cessation in Asian smokers	Korea; multicentre (5 sites), Taiwan (5 sites); Pfizer Inc.	12 wks; 24 wks	Varenicline vs. placebo	Wk-1 titration: 0.5 mg every day for 3 days, then 0.5 mg twice daily for 4 days Full dosage ( 1.0 mg BID) starting from day 8 Treatment phase: 1, 2, 3, 4, 6, 8, 10, 12 wks; with 5 telephone contacts (up to 5 min) at TQD + 3 days, then weeks 5, 7, 9, 11 Follow-up phase: 13, 16, 20, 24 wks All received educational booklet with counselling (up to 10 min), TQD coincided with wk-1 clinical visit	At each visit, participants provided self-reported abstinence during the past 7 days; CAR for wks 9-12; CAR for wks 9-24; 7-day pp for wks 12 and 24 Abstinence was verified by exhaled CO level $\leq 10$ ppm	Total: 250 / 243 (97.2%) / 237 (94.8%)
Wang (2009); <sup>51</sup> RCT, double-blind, parallel	To evaluate the efficacy of a standard regimen of varenicline compared with placebo for	China; multicentre (10 sites), Singapore (3 sites) and Thailand (2 sites); Pfizer Inc.	12 wks; 24 wks	Varenicline vs. placebo	Wk-1 titration: 0.5 mg every day for 3 days, then 0.5 mg twice daily for 4 days Full dosage ( 1.0 mg BID) starting from day 8	At all clinic visits, participants were assessed for vital signs, exhaled CO,	Total: 333 / 322 (96.7%) / 319 (95.8%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	smoking cessation in China, Singapore, and Thailand  Varenicline was efficacious for smoking cessation over treatment period and in follow-up period in Asian smokers				Treatment phase: 1, 2, 3, 4, 6, 8, 10, 11, 12 wks; and telephone contact wks 5 and 7 Follow-up phase: 13, 16, 20, 24 wks with telephone contact at wks 14, 18, 22 All received educational booklet and counselling (up to 10 min)	and their dosing record CAR for wks 9-12; CAR for wks 9-24; 7-day pp for wks 12 and 24	
Williams (2007); <sup>52</sup> RCT, double-blind, parallel	To assess the safety of long-term varenicline for smoking cessation  Varenicline was more effective smoking cessation aid than placebo. The dose of 1 mg BID was safe for up to 1 year	US; multicentre (8 sites), Australia (1 site); Pfizer	Treatment and follow-up: 52 wks	Varenicline vs. placebo	Varenicline: 0.5 mg QD in the evening on days 1 to 3; 0.5 mg BID on days 4 to 7; and 1mg BID starting on day 8 TQD: at wk 1 visit All received brief counselling (up to 10 min) Follow-up: wks 2, 12, 24, 36, and 52	Self-reported abstinence, verified by exhaled CO levels $\leq 10$ ppm 7-day PP abstinence at each follow-up visit	377 / NA / 194 (51.5%)
<b>Varenicline vs. bupropion vs. placebo</b>							
Gonzales (2006); <sup>54</sup> RCT, parallel (phase 3 trial)	To assess efficacy and safety of varenicline for smoking cessation compared with sustained-release bupropion and	US; multicentre (19 sites); Pfizer Inc.	12 wks; 52 wks	Varenicline vs. bupropion vs. placebo	Titration: Varenicline, 0.5 mg/d for days 1 to 3, 0.5 mg BID for days 4 to 7, then 1 mg BID through wk 12; bupropion, 150 mg/d for days 1 to 3, then 150 mg BID through wk	Self-reported abstinence and exhaled CO measurement $< 10$ ppm CAR for wks 9-12; CAR for	Total: 1025 / 699 (68.2%) / 584 (57%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	<p>placebo</p> <p>Varenicline was more efficacious than placebo and bupropion SR for smoking cessation over treatment period and in follow-up period</p>				<p>12. All received educational booklet and weekly counselling (<math>\leq 10</math> min) at each clinical visit</p> <p>Follow-up phase: 13, 24, 36, 44, and 52 wks with telephone contact at wks 16, 20, 28, 32, 40, and 48</p>	<p>wks 9-24; CAR for wks 9-52; 7-day pp for wks 12, 24 and 52</p>	
Jorenby (2006); <sup>55</sup> RCT, parallel (phase 3 trial)	<p>To determine the efficacy and safety of varenicline for smoking cessation compared with placebo or sustained-release bupropion</p> <p>Varenicline was more efficacious in smoking cessation for both short and long-term than placebo and bupropion SR</p>	US; multicentre (14 sites); Pfizer Inc.	12 wks; 52 wks	Varenicline vs. bupropion vs. placebo	<p>Wk-1 titration to full dose of varenicline (1 mg BID), bupropion (150 mg BID)</p> <p>All received educational booklet and weekly counselling (<math>\leq 10</math> min) at each clinical visit</p> <p>Follow-up phase: 13, 24, 36, 44, and 52 wks with telephone contact at wks 16, 20, 28, 32, 40, and 48</p>	<p>Self-reported abstinence and exhaled CO measurement of <math>&lt; 10</math> ppm</p> <p>CAR for wks 9-12; CAR for wks 9-24; CAR for wks 9-52; 7-day pp for wks 12, 24 and 52</p>	Total: 1027 / 722 (70.3%) / 665 (64.8%)
Nides (2006); <sup>56</sup> RCT, parallel (phase 2 trial)	<p>To evaluate the efficacy, tolerability, and safety of 3 varenicline doses for smoking cessation</p>	US; multicentre (7 sites); Pfizer Inc.	7 wks; 52 wks	Varenicline vs. bupropion vs. placebo	<p>Varenicline: 0.3 mg once daily, 1.0 mg once daily, or 1.0 mg BID</p> <p>Bupropion: 150 mg QD (days 1-3), then 150 mg BID through wk-7</p> <p>All received educational</p>	<p>Self-reported abstinence and exhaled CO measurement of <math>\leq 10</math> ppm</p> <p>CAR for any 4 wks (28-day</p>	Total: 638 / 433 (67.9%) / 353 (55%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	compared with bupropion and placebo  Varenicline demonstrated both short and long-term efficacy versus placebo				booklet and weekly counselling ( $\leq 10$ min) at each clinical visit Follow-up phase: 12, 24, and 52 wks with telephone contact every 4 wks beginning at wk-16	period); CAR for wks 4-7; CAR for wks 4-12; CAR for wks 4-24; CAR for wks 4-52	
<b>Varenicline vs. nicotine patch</b>							
Aubin (2008); <sup>57</sup> RCT, parallel	To compare a 12-wk standard regimen of varenicline with a 10-wk standard regimen of transdermal nicotine replacement therapy (NRT) for smoking cessation  The long-term efficacy of varenicline and nicotine patch was similar	Belgium; multicentre (4 sites), France (6 sites), The Netherlands (4 sites), UK (4 sites) and USA (6 sites); Pfizer Inc.	Varenicline: 12 wks; 52 wks NRT: 10 wks; 52 wks	Varenicline vs. nicotine patch	Target quit date: after wk-1 Varenicline: 0.5 mg QD for 3 days, 0.5 mg BID for 4 days, then 1 mg BID through wk-12 Patch: 21 mg QD for 6 wks, 14 mg QD for 2 wks, 7 mg QD for 2 wks. During treatment phase, all received telephone call 3 days after TQD and visited clinic weekly Follow-up phase: 13, 16, 24, 32, 40, 48 and 52 wks with telephone contact at wks 14, 20, 28, 36, and 44	CAR confirmed by CO levels $\leq 10$ ppm Varenicline: CAR for wks 9-12, 9-24, 9-52 NRT: CAR for wks 8-11, 8-24, 8-52 7-day pp for wks 24 and 52	757 / 595 (78.6%) / 477 (63%)
<b>Nicotine patch vs. placebo</b>							
Campbell (1996); <sup>71</sup> RCT, parallel	To assess the efficacy of transdermal nicotine as an	UK; hospital, in-patient/out-patient (1 site); Ciba-Geigy Ltd	12 wks; 52 wks	Nicotine patch (all day) vs. placebo	Patch: 30 cm <sup>2</sup> (21 mg QD), 20 cm <sup>2</sup> (14 mg QD) and 10 cm <sup>2</sup> (7 mg QD) Placebo: 13% of the	CAR confirmed by CO levels $\leq 7$ ppm	234 / 121 (51.7%) / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	<p>adjunct to advice and support in helping patients attending hospital with smoking-related disease to stop smoking</p> <p>Nicotine patch had higher success rates in helping hospitalized patients quit smoking</p>				<p>active form</p> <p>Treatment phase: all returned to the outpatient clinic at 2, 4, 8, and 12 wks; dosage altered at each visit according to smoking status. All received counselling (30-60 min) at first visit and support at each visit</p> <p>Follow-up: at 12 wks, 6 months and 12 months.</p> <p>Patients smoking at 12 wks were not followed-up</p>	CAR for wk 12 and months 6 and 12	
Davidson (1998); <sup>58</sup> RCT, double-blind, parallel	<p>To evaluate the efficacy and safety of a transdermal nicotine patch as an aid for smoking cessation in an over-the-counter setting</p> <p>Nicotine patch obtained over-the-counter was efficacious in smoking cessation compared with placebo</p>	US; shopping malls, over-the-counter (4 sites); Elan Pharmaceutical Research Corp.	6 wks; 24 wks	Nicotine patch (all day) vs. placebo	<p>Interested individuals were referred to the market research centre located at each mall, which did the screening and data collection on a weekly basis throughout the treatment period and follow-up.</p> <p>Patch: 22 mg QD</p> <p>All received self-help booklet and were asked to keep record of smoking behaviour on a diary card</p>	<p>Smoking behaviours; diary cards; CO levels <math>\leq 8</math> ppm</p> <p>CAR for wks 3-6</p> <p>7-day pp for wks 6 and 24</p>	802 / 261 (32.5%) / NR
Daughton (1991); <sup>59</sup> RCT, double-	To assess the smoking cessation efficacy of	US; medical centres (2 sites); ALZA Corp.	4 wks; 11 months	Nicotine patch (24 h) vs. Nicotine patch	15 cm <sup>2</sup> patch 24 h patch: one patch with nicotine and one	Self-reported abstinence, confirmed by	158 / NR / NR

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blind, parallel	transdermal nicotine patches as an adjunct to low intensity therapy  Nicotine patch enhanced smoking cessation rates and reduced withdrawal symptoms			(16 h, daytime) vs. placebo	with placebo: placebo patch removed at bedtime 16 h patch (daytime): one patch with nicotine and one with placebo: nicotine patch removed at bedtime Placebo: two placebo patches All received brief smoking counselling (individual or group), and follow-up procedures on a weekly basis	CO levels $\leq$ 8 ppm	
Daughton (1998); <sup>60</sup> RCT, double-blind, parallel	To evaluate the smoking cessation efficacy of nicotine patch therapy as an adjunct to low-intensity, primary care intervention  Nicotine patch therapy enhanced quit rates as an adjunct to brief primary care intervention	US; family practices (21 sites); Marion Merrell Dow Inc.	10 wks; 12 months	Nicotine patch vs. placebo	Patch (10-wk regimen): 6 wks of 21 mg, 2 wks of 14 mg and 2 wks of 7 mg  Participants received a support booklet Telephone contact for follow-up visits at 3, 6, and 12 months Participants received \$75 honorarium if they came to the site to relate their experiences with the patch at 3 months	Self-reported abstinence, confirmed by CO levels $\leq$ 8 ppm	369 / NR / 361

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
Fiore (1994); <sup>61</sup> RCT, double-blind, parallel	To assess the effectiveness of transdermal nicotine therapy for smoking cessation and suppression of withdrawal severity in conjunction with two different adjuvant counselling treatments  Nicotine patch was efficacious with two different types of counselling for smoking cessation	<u>Study 1:</u> US; multicentre (4 sites); Elan Pharmaceutical Research Corporation	8 wks; 6 months	Nicotine patch vs. placebo	Screening: 10 min motivational message from the physician 8 wks of 22 mg nicotine patch (or placebo) Participants received weekly group counselling (1 h), efficacy assessment and vital sign check-up	Self reported abstinence, verified by CO levels <10 ppm	87 / 77 (88.5%) / 62 (71.3%)
		<u>Study 2:</u> US (1 site); Elan Pharmaceutical Research Corporation	6 wks; 6 months	Nicotine patch vs. placebo	Screening: 10 min motivational message from the physician 4 wks of 22 mg nicotine patch (or placebo), then 2 wks of 11 mg nicotine patch (or placebo) Participants received weekly individual counselling (~15 min), efficacy assessment and vital signs check-up	Self reported abstinence, verified by CO levels <10 ppm	112 / 79 (70.5%) / 72 (64.3%)
Glavas (2003); <sup>75</sup> RCT, double-blind, parallel	To assess the smoking prevalence and efficacy of nicotine replacement therapy on the quitting rate of health care workers after 3 wks therapy and after 1- and 5-year follow-up	Croatia; university hospital (1 site); Novartis donated nicotine patches	3 wks; 1 year and 5 years	Nicotine patch vs. placebo	3 different patch sizes (30, 20, 10 cm <sup>2</sup> ), delivering 0.7 mg/cm <sup>2</sup> nicotine per 24 h Heavy smokers (≥20 cigarettes per day): 30 cm <sup>2</sup> size; Medium smokers (10-19 cigarettes per day): 20 cm <sup>2</sup> size; Light smokers (<10 cigarettes per day): 10 cm <sup>2</sup> size	CO content of exhaled breath (quitters: <11 ppm; non-quitters: ≥11 ppm)	112 / 107 (95.5%) / 107 (95.5%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	Short term nicotine patch treatment was effective, but the effects waned over time and the relapse rate was high				Follow-up: 12 months and 5 years		
Hays (1999); <sup>62</sup> RCT, double-blind, parallel	To determine the efficacy and safety of the nicotine patch for smoking cessation in an over-the-counter environment  The over-the-counter nicotine patch was effective and safe for smoking cessation	US; multicentre (3 sites); Elan Pharmaceutical Research Corp.	6 wks; 24 wks	Nicotine patch vs. placebo	Treatment: 22 mg QD nicotine patch or placebo for 6 wks Follow-up: 12, 24 wks All received instructions for patch use and self-help pamphlet, with no counselling or advice	Self reported abstinence, verified by CO levels $\leq 8$ ppm	643 / NR / NR
Hughes (2003); <sup>63</sup> RCT, parallel	To assess the efficacy of the nicotine patch in smokers with a history of alcoholism Nicotine patch was an effective treatment for smoking cessation in smokers with history of alcoholism	US; multicentre (2 sites); Glaxo-SmithKline provided patches	12 wks; 26 wks	Nicotine patch vs. placebo	Treatment: 21 mg/24h nicotine patch for 6 wks, then 14 mg/day for 2 wks, 7 mg/d for 2 wks and placebo for 2 wks Placebo: placebo patches for 12 wks All received stop smoking booklet and group behavioural therapy (1h) at each of the first 6 wks	Self reported abstinence, verified by CO levels $< 10$ ppm	115 / NR / NR

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Hurt (1994), <sup>64</sup> RCT, double-blind, parallel	To determine the efficacy of a 22-mg nicotine patch combined with physician advice and nurse follow-up in 1-year smoking cessation outcome  Nicotine patch combined with physician advice and nurse follow-up was an effective treatment for smoking cessation	US; multicentre (3 sites); Lederle Laboratories	8 wks; 1 year	Nicotine patch vs. placebo	Treatment: 22-mg nicotine patch for 8 wks  Follow-up: 6, 9, 12 months  All received stop smoking booklet, brief individual counselling; weekly follow-up telephone call by study nurse	Self reported abstinence, verified by CO levels $\leq 8$ ppm  Pp weekly for 8 wks, then at months 6, 9, 12	240 / 196 (81.7%) / NR
ICR group (1993, 1994, 2003), <sup>72,355,356</sup> RCT, double-blind, parallel	To assess the effectiveness of transdermal nicotine patches in helping heavy smokers to stop smoking  Nicotine patch was effective in general practice setting with nursing support, both short and long-term	UK; general practices (19 sites); Ciba-Geigy Pharmaceuticals	12 wks; 1 year, 8 years	Nicotine patch vs. placebo	Treatment: 30 cm <sup>2</sup> (21 mg) patch for 4 wks, 20 cm <sup>2</sup> (14 mg) patch for 4 wks and then 10 cm <sup>2</sup> (7 mg) patch for 4 wks Participants received pamphlets or booklets on smoking cessation Follow-up: 24 wks, 52 wks, 8 years	Self reported abstinence, verified by CO levels $\leq 10$ ppm, salivary cotinine concentration $\leq 113.5$ nmol/L (20 ng/ml)	1686 / 720 (42.7%) / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
Killen (1997); <sup>65</sup> RCT, parallel	To examine the treatment efficacy of nicotine patches in smoking cessation  The efficacy of nicotine patch decreased over time	US (No. of sites NR); Hoechst Marion Roussel Inc. provided patches	16 wks; 12 months	Nicotine patch vs. placebo	Treatment: 22 mg/day for 8 wks, 14 mg for 4 wks, and then 7 mg for 4 wks Participants received manual booklet or booklet and video (20 min) on smoking cessation Follow-up: 2, 6, and 12 months	Self reported abstinence, verified by CO levels <9 ppm, salivary cotinine concentration < 20 ng/ml	424 / NR / NR
Lewis (1998); <sup>66</sup> RCT, parallel	To assess the safety and efficacy of a treatment involving brief counselling and the nicotine patch among hospital inpatients  Nicotine patch showed no superiority over placebo in treatment of smoking cessation among hospitalized patients	US; hospital (1 site); Elan Pharmaceutical Research Corporation	6 wks; 6 months	Nicotine patch vs. placebo	Treatment: 22 mg/day for wks 1-3 or identical placebo patches; 11 mg/day for wks 4-6 All received pamphlets and counselling on smoking cessation from the physician at the initial visits and from the nurse by telephone at 1, 3, 6, and 24 wks after the initiation of patch treatment	Self reported abstinence, verified by CO levels ≤10 ppm at 6 months only 7-day PP abstinence at 1, 3, and 6 wks, and 6 months	124 / NR / NR
Oncken (2007); <sup>67</sup> RCT, double-blind, parallel	To examine the efficacy of transdermal nicotine in postmenopausal smokers	US (1 site); Glaxo-SmithKline provided patches	12 wks; 1 year	Nicotine patch vs. placebo	Treatment: 12 wks (21 mg), 7 visits All received group counselling sessions (~2h) during visits 2-5 At visit 7, subjects were	Self reported abstinence, verified by CO levels ≤8 ppm 7-day pp abstinence for	152 / NR / 119 (78.3%)

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	Nicotine patch did not improve long-term abstinence rates among postmenopausal women				instructed to titrate down (14 mg for 2 wks, then 7 mg for 2 wks) Follow-up : 1 year after treatment	wks 52	
Paoletti (1996); <sup>76</sup> RCT, double-blind, parallel	To investigate the effect on outcome of different doses of transdermal nicotine replacement after stratification according to baseline plasma cotinine values  Nicotine patch therapy was associated with higher success rates in smokers with low baseline cotinine values	Italy (1 site); Pharmacia	12 wks (and 6 wks tapering); 1 year	Nicotine patch vs. placebo	Two groups: a) Cotinine $\leq$ 250 ng/ml: 15mg/16h patch or placebo patch b) Cotinine $>$ 250 ng/ml: 15mg/16h or 25 mg/16h patch  Both cotinine groups: 6 wks tapering of 10 mg for 3 wks, then 5 mg for 3 wks Visits at wks 1, 3, 6, 12, and 18, and at 12 months All received brief advice (10 min) on health effects of smoking and on nicotine addiction	Self reported abstinence, verified by CO levels $<$ 10 ppm CAR at wks 1 up to 12 months	297 / 175 (58.9%) / 97 (32.6%)
Richmond (1994, 1997, 2007); <sup>77,357-359</sup> RCT, double-blind, parallel	To evaluate the efficacy of the transdermal nicotine patch as an aid to smoking cessation when used as an adjunct to a cognitive-	Australia (1 site); Marion Merrell Dow	10 wks; 3- 6 months, 1-10 years	Nicotine patch vs. placebo	Treatment: 21 mg/day for 6 wks, 14 mg/day for 2 wks, then 7 mg/day for 2 wks. Placebo patch had 1 mg nicotine All received weekly cognitive-behavioural smoking cessation	Self reported abstinence, verified by CO levels $\leq$ 10 ppm 7-day pp abstinence at 3 months, at 6	313 / NR / NR

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	behavioural group intervention  Nicotine patch was effective when used as an adjunct to a group cognitive-behavioural intervention				program (2h group sessions), for 5 consecutive weeks Follow-up: 3 months, 6 months, 1 year, 2 years, 3 years, 7 years and 10 years	months CAR at 3 months, at 6 months,	
Russell (1993); <sup>73</sup> RCT, double-blind, parallel	To evaluate the efficacy of transdermal nicotine patches as an aid to stopping smoking  Nicotine patch used as an adjunct to brief advice and support in a general practice setting was an effective aid to long term cessation of smoking in heavy smokers	UK; general practices (30 sites in 15 counties); Kabi Pharmacia AB	18 wks; 52 wks	Nicotine patch vs. placebo	Patch: 30 cm <sup>2</sup> (15 mg/16 h), 20 cm <sup>2</sup> (10 mg/16 h) and 10 cm <sup>2</sup> (5 mg/16 h) Treatment: 12 wks treatment and six wks weaning (either gradual or abrupt) Placebo: patch with no nicotine All received brief advice and booklet on smoking cessation Follow-up: wks 26 and 52	Self reported complete abstinence from wk 3 to 1 year, validated by CO concentration <10 ppm at wks 3, 6, 12, 26, and 52	600 / NR / NR
Sachs (1993); <sup>68</sup> RCT, double-blind, parallel	To determine the effectiveness of a 16-hour transdermal nicotine patch in assisting smokers	US (1 site); Kabi Pharmacia AB and Parke-Davis	18 wks; 52 wks	Nicotine patch vs. placebo	Treatment: 12 wks with patch (30-cm <sup>2</sup> , 15 ± 3.5 mg/16 h) Tapering: 3 wks with 20-cm <sup>2</sup> patch, and 3 wks with 10 cm <sup>2</sup> patch	Self reported completed abstinence, verified by CO levels ≤9 ppm at each visit,	220 / NR / NR

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	to stop smoking, when used in a primary medical practice model  The 16-hour transdermal nicotine patch provided a safe and effective treatment for both short and long term smoking cessation				All received brief individual smoking cessation advice (5-10 min) at each visit Visits after TQD: 1, 2, 3, 6, 12, 15, 18, 26, 52 wks	serum cotinine level $\leq 15$ ng/ml at each visit after 18 wks	
Stapleton (1995); <sup>74</sup> RCT, double-blind, parallel [same study as Russell (1993) <sup>73</sup> with full sample]	To evaluate the efficacy of transdermal nicotine patches as an aid to stopping smoking  Nicotine patch was more effective than placebo up to 1 year of follow-up	UK; general practices (30 sites in 15 counties); Kabi Pharmacia AB	18 wks; 52 wks	Nicotine patch vs. placebo	Patch: 30 cm <sup>2</sup> (15 mg/16 h), 20 cm <sup>2</sup> (10 mg/16 h) and 10 cm <sup>2</sup> (5 mg/16 h) Treatment: 12 wks treatment and six wks weaning (either gradual or abrupt) Placebo: patch with no nicotine All received brief advice and booklet on smoking cessation Follow-up: wks 26 and 52	Self reported complete abstinence from wk 3 to 1 year, validated by CO concentration <10 ppm at wks 3, 6, 12, 26, and 52	1200 / NR / NR
Tonnesen (1991, 1992); <sup>360,361</sup> Mikkelsen (1994); <sup>78</sup> RCT, double-blind, parallel	To examine the safety and efficacy of a 16-h nicotine patch in smoking cessation when used for up to 16 wks	Denmark (No. of sites NR); Kabi Pharmacia Therapeutics	16 wks; up to 3 years	Nicotine patch h vs. placebo	Treatment: 30 cm <sup>2</sup> nicotine patch (releasing $15 \pm 3.5$ mg nicotine in 16 h) or placebo. Patch was applied in the morning and removed at bedtime. After 12 wks, 20	Self reported completed abstinence, verified by CO levels $\leq 10$ ppm	289 / NR / NR

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	Nicotine patch therapy was safe and more effective than placebo				patches of 20 cm <sup>2</sup> and 20 patches of 10 cm <sup>2</sup> were given for additional 4 wks TQD: first visit Visits and follow-up visits: wks 3, 6, 12, 26, and 52, years 2 and 3		
Tonnesen (1999); <sup>80</sup> RCT, double-blind, parallel [CEASE]	To determine whether high dosage and longer duration of nicotine patch therapy would increase the success rate  Higher dose of nicotine patch was associated with an increase of long-term success in smoking cessation	17 European countries; clinical centres (36 sites); Pharmacia & Upjohn	8 wks or 22 wks; 12 months	Nicotine patch vs. placebo	Treatment and down titration: 5 groups a) 25 mg patches for 22 wks, 15 mg for 2 wks and 10 mg for 2 wks b) 25 mg patches for 8 wks, 15 mg for 2 wks and 10 mg for 2 wks c) 15 mg patches for 22 wks, 10 mg for 4 wks d) 15 mg patches for 8 wks, 10 mg for 4 wks e) Placebo patches for 26 wks  Visits at weeks 1, 2, 4, 8, 12, 22, 26, 52	Self reported completed abstinence, verified by CO levels <10 ppm  Plasma nicotine and cotinine at wks 4, 8, 22, 52	3575 / 1506 (42%) / 1792 (50%)
TNS group (1991, 1999); <sup>69,362</sup> RCT, double-	To evaluate the efficacy of a new transdermal nicotine system for	US; multicentre (9 sites); Alza Corp., Marion Merrell Dow Inc.	12 wks (6 wks treatment, 6 wks down	Nicotine patch vs. placebo	Treatment: 6 wks on one of 21-mg, 14-mg or 7-mg transdermal nicotine or placebo	Self reported completed abstinence, verified by CO	935 / 700 (74.9%) at 6 wks / NR

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blind, parallel	smoking cessation  Nicotine patch therapy at high dose (21 mg/day) showed higher long-term success rates compared to lower doses and placebo		titration); 4 to 5 years		Down titration: 6 wks for abstainers only Follow-up: 6-, 12-, 24-, 36-, and ≥48-month All received booklet and group behavioural support (45-60 min) on smoking cessation	levels ≤8 ppm during each visit after 2 wks	
Westman (1993); <sup>70</sup> RCT, double-blind, parallel	To determine the efficacy of the nicotine patch in smoking cessation when combined with self-help materials, 3 brief visits and telephone counselling  Nicotine patch combined with self-help materials, brief visits and telephone counselling was efficacious in smoking cessation	US (1 site); TBS Laboratories	6 wks; 6 months	Nicotine patch vs. placebo	Treatment: 2 patches (15 cm <sup>2</sup> patch) delivering 25 mg nicotine per day for 4 wks; 1 patch (15 cm <sup>2</sup> ), delivering 12.5 mg/d for next 2 wks Placebo: patch looked and smelled the same All received self-help materials and telephone counselling Follow-up: 4 wks, 6 wks and 6 months	Self reported complete abstinence, verified by CO levels <8 ppm CAR at 6 wks, 3 months and 6 months	159 / 129 (81%) / NR
Wisborg (2000); <sup>79</sup> RCT, parallel	To assess the effect of nicotine patches on smoking cessation in	Denmark (1 site); Pharmacia and Upjohn provided nicotine patches	11 wks; 1 year postpartum	Nicotine patch vs. placebo	Treatment: 15-mg patches (16 h/day) for 8 wks and 10-mg patches (16 h/day) for 3 wks	Self reported completed abstinence, verified by	250 / NR / NR

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	pregnant women  Nicotine patch had no influence on smoking cessation during pregnancy				Follow-up visits: at wks 8, 11 and 4 wks before the expected delivery date All received brief advice and pamphlet on smoking cessation; all were offered 4 individual prenatal visits with a midwife and 2.5 hrs of counselling	salivary cotinine level < 26 ng/ml	
<b>Nicotine gum vs. placebo</b>							
Ahluwalia (2006); <sup>81</sup> RCT, double-blind, parallel	To evaluate the efficacy of nicotine gum (2 mg vs. placebo) and counselling (motivational interview vs. health education) for African American light smokers  The quit rates for nicotine gum was no better than placebo group at 6 months	US (1 site); Government; Glaxo-SmithKline provided study medication	8 wks; 26 wks	Nicotine gum + education vs Nicotine gum + interview vs. Placebo + education vs. Placebo + interview	Treatment: 8 wks with 2 mg nicotine gum or placebo. <ul style="list-style-type: none"> <li>8-10 cigarettes per day: 4 wks with 10 pieces of gum, 2 wks with 8 pieces and 2 wks with 6 pieces</li> <li>5-7 cigarettes per day: 4 wks with 8 pieces of gum, 2 wks with 6 pieces and 2 wks with 4 pieces</li> <li>&lt;5 cigarettes per day: 4 wks with 6 pieces of gum, 2 wks with 4 pieces and 2 wks with 2 pieces</li> </ul>	Abstinence at wk 26 was verified by salivary cotinine level of ≤20 ng/ml and CO level of ≤10 ppm	755 / 603 (79.9%) / 637 (84.4%)

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					All received booklet on smoking cessation, and either a motivational interview or health educational counselling Total of 6 counselling sections, about 20 min each		
Areechon (1988); <sup>99</sup> RCT, parallel	To evaluate the efficacy of nicotine chewing gum for smoking cessation among smokers in Thailand  Nicotine gum could alleviate withdrawal symptom and encourage abstinence	Thailand (No. of sites: NR): Merrell Dow and A.B. Leo	NR (each received 840 pieces of gum, considered sufficient for 2-3 months); 6 months	Nicotine gum vs. placebo	Treatment: Participants were instructed to chew gum as soon as felt the urge to smoke; not exceed 20 pieces daily All received leaflet on the use of gum and smoking cessation Weekly visits, seen by a physician Follow-up: 6 months	Self reported abstinence was verified by CO levels (cut-off: NR)	199 / NR / NR
Batra (2005); <sup>100</sup> RCT, double-blind, parallel	To evaluate the efficacy of nicotine gum in helping smokers reduce or quit smoking  Nicotine gum may help not-ready-to-quit smokers to reduce smoking and promote smoking cessation	Germany and Switzerland (2 sites); Pfizer Consumer Healthcare	12 months; 13 months	Nicotine gum vs. placebo	Treatment: 4-mg nicotine gum or placebo; use as desire for up to 12 months; 6-24 pieces daily; goal was to reduce smoking and to substitute nicotine in cigarettes with the nicotine in gum Clinic visits: 6 wks, 4 months and 12 months	Self reported abstinence was verified by CO levels <10 ppm	364 / NA / 249 (68.4%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
Blondal (1989); <sup>101</sup> RCT, double-blind, parallel	To investigate the effect of 4-mg nicotine gum for smoking cessation  Nicotine gum could be an effective aid in stopping smoking, particularly among heavy smokers	Iceland (1 site); Government	3 months; 2 years	Nicotine gum vs. placebo	Treatment: People were encouraged to use as much gum (4 mg) as necessary to be able to abstain from smoking, and to gradually diminished the dose and finally stop, within 3 months All received booklets and 5 group sessions (1h each) on smoking cessation	Self reported abstinence was verified by exhaled CO levels <10 ppm, or by CO hemoglobin of <2.1%	182 / NR / NR
Clavel-Chapelon (1997); <sup>102</sup> RCT, parallel	To estimate the smoking cessation rates 4 years after treatment with nicotine gum  The efficacy of nicotine gum sharply decreased over time, and did not offer any long-term improvement over placebo	France (No. of sites NR); CIBA-GEIGY supplied the gum	1-6 months; 4 years	Nicotine gum vs. placebo	Treatment: 2-mg nicotine gum; people used gum from 1-6 months. The maximum number of pieces of gum allowed per day during the first 6 months was 30. Only ex-smokers on Day 28 were considered successes and were follow-up every 3 months during the first year and subsequently after 2 and 4 years	Self reported abstinence was verified by exhaled CO levels (cut off: NR)	996 / NR / NR
Cooper (2005); <sup>82</sup> RCT, parallel	To assess the efficacy of nicotine gum in addition to a 13-wk cognitive behavioural smoking cessation program targeted	USA (No. of sites NR); sponsor NR	13 wks; 12 months	Nicotine gum vs. placebo	Treatment: 2-mg nicotine gum; supplied 16 pieces of gum per day; on an as needed basis; instructions to chew 10-12 pieces per day and no more than one piece of gum per hour.	Point prevalence abstinence, verified by CO <10 ppm	294 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	to women  Nicotine gum treatment had no effect on cessation rates and post cessation weight gain				Weaning of gum took place on wks 11 through 13 by reducing the amount of gum chewed by 33% each week Follow-up: 6 and 12 months All received group behavioural support (~1h) on a weekly basis up to wk 5 (TQD)		
Fagerström (1982); <sup>95</sup> RCT, double-blind, parallel	To assess the efficacy of nicotine gum in smoking cessation  Nicotine gum was efficacious up to 6 months after quitting compared with placebo	Sweden (1 site); sponsor NR	4 wks to approximately 3 months; 6 months	Nicotine gum vs. placebo	Treatment: 2-mg nicotine gum; administered ad-lib for about 4 wks; patients were then encouraged to reduce, and, finally, eliminate use Follow-up: 6 months; point prevalence verified at months 1, 3, and 6 All received individual counselling; average 7.7 sessions per patient Patients took part in a comprehensive smoking cessation program	Point prevalence abstinence, verified by CO $\leq 4$ ppm	100 / 96 / 96
Fortmann (1988); <sup>83</sup> RCT, double-blind, parallel	To determine the effectiveness of nicotine gum with self-administered relapse prevention materials in maintaining	US; multicentre (3 sites); Government and Merrell Dow	9 wks; 6 months	Nicotine gum vs. placebo	Treatment: 2-mg nicotine gum; administered ad-lib for 4 wks; patients were then encouraged to reduce, and, finally, eliminate use by wk 9; Maximum of 30 pieces of	Self-reported abstinence, verified by cotinine concentrations $\leq 20$ $\mu\text{g/L}$ 7-day pp	300 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	smoking cessation Combined therapy of nicotine gum and minimal contact psychological intervention produced higher abstinence rates after six months than either placebo gum or no gum				gum per day was set Follow-up: 6 months Self-help relapse prevention modules were mailed each wk, for 8 wks	abstinence at 6 months	
Garvey (2000); <sup>84</sup> RCT, parallel	To investigate the efficacy of nicotine gum (2 mg and 4 mg) in smoking cessation for low and high nicotine-dependent subjects  Nicotine gum was more efficacious than placebo. There was no difference between high and low doses	US (No. of sites NR); Government and Merrell Dow (supplied the nicotine gum)	2 months and weaning off up to 5 months; 1 year	Nicotine gum vs. placebo	Treatment: Two subgroups (low- and high-nicotine dependent). Participants in each subgroup were randomized to 2-mg, 4-mg or placebo gums; they were instructed to use 9-15 pieces of gum per day (not less than 6 pieces and not exceeding 20 pieces per day) for 2 months, then wean themselves off 1 piece of gum each day; participants should be weaned off gum by 5 months Follow-up visits: 1, 7, 14, and 30 days, and again 2, 3, 6, 9, and 12 months All received brief	Self-reported abstinence, verified by and CO levels $\leq 8$ ppm	608 / NR/ NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
					behavioural counselling (5-10 min) in all visits		
Hall (1987); <sup>85</sup> RCT, parallel  (same study in gum vs. gum + behaviour)	To assess the efficacy of 2-mg nicotine gum and behavioural support in smoking cessation  Nicotine gum was more effective than placebo. Interactions between gum and behavioural conditions were not significant	US (No. of sites NR); Government	Up to 1 year; 1 year	Nicotine gum vs. placebo vs. Nicotine gum + behaviour vs. placebo + behaviour	Treatment: 2 mg gum was available for 1 year from the beginning of treatment Participants were randomized to 4 arms: gum, placebo, gum + behavioural support, and placebo + behavioural support Follow-up visits: wks 3, 12, 26, and 52 14 sessions of behavioural support (75 min each)	Self-reported abstinence, verified by CO levels <8 ppm or serum thiocyanate levels <95 mg/ml	139 / NR / 128
Hall (1996); <sup>86</sup> RCT, parallel	To assess the efficacy of nicotine gum in smoking cessation in smokers with and without a history of major depressive disorders  Nicotine gum was no more effective than placebo	US (1 site); Government	8 wks plus 4 wks tapering; 52 wks	Nicotine gum vs. placebo	Treatment: 2-mg gum or placebo; participants were directed to chew at least one piece of gum per hour for at least 12 h/day during the first 3 wks; gum was supplied to be used as needed for the next 5 wks; enough gum was given to taper use during the following 4 wks Participants received either mood management intervention or health education intervention Follow-up: 12, 26 and 52 wks	Self-reported abstinence, verified by urine cotinine levels ≤ 60 ng/ml or CO levels ≤ 10 ppm	201 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
Herrera (1995); <sup>103</sup> RCT, double-blind, parallel	To study the effectiveness of nicotine gum in combination with a behaviour modification program for smoking cessation  2-mg nicotine gum was superior to placebo for medium/low-dependent smokers and 4-mg gum is superior to 2-mg gum for high-dependent smokers	Venezuela and Sweden (2 sites); sponsor NR	3 months; 2 years	Nicotine gum m (2 mg) vs. placebo (for low-dependent smoking)  Nicotine gum (2 mg) vs (4 mg) (for high-dependent smoking)	Treatment: 2-mg, 4-mg gum or placebo; highly-dependent smokers were randomized to receive either 2-mg or 4-mg dose; low-dependent smokers were randomized to receive either 2-mg or placebo gum. All received 12 group sessions of behavioural support, 2 sessions per wk, each lasting 60-80 min; individual session were available at 6, 12, and 24 months	Self-reported abstinence, verified by CO levels $\leq$ 6 ppm	322 / NR / NR
Hjalmarson (1984); <sup>96</sup> RCT, double-blind, parallel	To study the effect of 2-mg nicotine gum as an adjunct to group therapy for smoking cessation  Nicotine gum was effective in improving success rates	Sweden (1 site); sponsor NR	Gum use up to 6 months; 1 year	Nicotine gum vs. placebo	Treatment: 2-mg nicotine or placebo gum All received weekly group behavioural therapy (6 wks) given by one physician and two psychologists	Self-reported abstinence, verified by CO (cut-off levels: NR)	206 / NR / NR
Hughes (1989); <sup>87</sup> RCT, double-blind, parallel	To evaluate the efficacy of nicotine gum in smoking cessation in a group of smokers	US; family practice clinics (2 sites); Government; Merrell Dow provided gum	Gum use up to 12 months	Nicotine gum vs. placebo	Treatment: 2-mg gum or placebo; gum use ad lib; 3 months after quit date, participants were reminded to stop gum use	Self-reported abstinence, verified by breath CO (<10 ppm),	315 / NR / 260 (83%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	attending a family practice clinic  Nicotine was not effective compared to placebo when used in a non-selected group with a brief intervention in a general medical practice				by slowly tapering use over the next month; some accessed gum for 12 months All received a booklet on gum information and smoking cessation, 10-12 min of individual advice from the nurse, 6-10 min of physician advice; total amount of intervention was 29-35 min Follow-up: 1, 6, and 12 months	saliva cotinine ( $\leq 15$ ng/ml) and saliva thiocyanate ( $< 1.6$ mmol/L)  CAR for 6 and 12 months	
Jamrozik (1984); <sup>92</sup> RCT, double-blind, parallel	To examine the effectiveness of nicotine gum for smoking cessation in general practice The effect of nicotine gum was small when used in general practice	UK; general practices (6 sites); Government; Lundbeck Limited provided all gum	At least 3 months; 6 months	Nicotine gum vs. placebo	Treatment: 2-mg gum or placebo; participants were instructed to use gum for at least 3 months (approximately 10 pieces/day; not to exceed 20 pieces/day), with tapering after 3 to 4 months, and complete cessation by 6 months Follow-up appointments: 2, 4, and 12 wks, and 6 months	Self-reported abstinence, verified by breath CO levels (cut-off: NR)	200 / NR / 197
Jarvis (1982); <sup>93</sup> RCT, double-blind, parallel	To examine the effectiveness of 2-mg nicotine gum as an aid to stopping smoking compared with	UK (1 site); Government; A B Leo supplied all gum	At least 3 months; 1 year	Nicotine gum vs. placebo	Treatment: 2-mg nicotine gum versus 1-mg nicotine gum (placebo); encouraged to stop smoking on the first day of chewing the gum; no	Self-reported abstinence, verified by breath CO levels (cut-off: NR)	116 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	<p>placebo containing 1 mg nicotine</p> <p>Nicotine gum reduced withdrawal symptoms and provided higher rate of abstinence than placebo</p>				<p>restriction on the amount of gum use; use gum for at least 3 months</p> <p>All received same instructions about the gum</p> <p>Follow-up: 3, 6 and 12 months</p>		
Kinnunen (2008); <sup>88</sup> RCT, parallel	<p>To investigate the role of nicotine gum and pre-treatment depressive symptoms in long-term smoking cessation</p> <p>Nicotine gum was better than placebo in both non-depressed and depressed smokers. The depressed ones were less successful</p>	US (No. of sites NR); Government; Aventis provided all gum	NR; 1 year	Nicotine gum vs. placebo	<p>Treatment: 2-mg or 4-mg nicotine gum or placebo gum.</p> <p>Follow-up: 1, 7, 14, 30, 60, 90, 180, 270 and 365 days</p> <p>All received brief counselling at each visit</p>	Self-reported abstinence, verified by CO levels <8 ppm CAR at 1 year	608 / NR / NR
Malcolm (1983); <sup>94</sup> RCT, double-blind, parallel	<p>To assess the role of nicotine gum as an aid to stopping smoking</p> <p>Nicotine gum was</p>	UK (No. of sites NR); A B Leo & Company	At least 3 months; 6 months	Nicotine gum vs. placebo	Treatment: 2-mg nicotine gum or placebo; chew at least 10 pieces of gum per day, for 30 min each, especially when desire to smoke was felt	Self-reported abstinence, verified by carboxy-hemoglobin of ≤1.6%	136 / NR/ NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	more successful than placebo or control group				Follow-up: weekly for first month; those who were not smoking at 1 month were followed-up for another 6 months All received brief counselling at each visit		
Oncken (2008); <sup>89</sup> RCT, double-blind, parallel	To estimate the safety and efficacy of treatment with 2-mg nicotine gum for smoking cessation during pregnancy  Nicotine gum did not increase quit rates during pregnancy	US; multicentre (3 sites); Government; Glaxo-SmithKline provided all gum	6 wks treatment and 6 wks taper; 6-12 wks after delivery	Nicotine gum vs. placebo	Treatment: 2-mg nicotine gum or placebo; chew one piece of gum for every cigarette smoked per day, not more than 20 pieces of gum per day; 6 wks of treatment and 6 wks taper period All received two, 35-min counselling sessions Follow-up: 1, 2, 3, and 6 wks, and 32-34 wks of gestation, and 6-12 wks postpartum	Self-reported abstinence, verified by CO levels <8 ppm 7-day pp at 6 wks, 32-34 wks of gestation, 6-12 wks after delivery	194 / NR / NR
Schneider (1983); <sup>90</sup> RCT, double-blind, parallel	To investigate the efficacy of nicotine gum in smoking cessation (with or without clinic support)  Nicotine gum was superior over placebo at six months, but the difference was less	US; multicentre (2 sites); Government; Merrell Dow and A B Leo supplied all gum	Participants decided length of treatment; 1 year	Nicotine gum vs. placebo	Treatment: gum used ad lib; dosage and details of treatment NR Follow-up: 3, 6, and 12 months	Self-reported abstinence, verified by CO (cut-off level: NR)	96 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	apparent at one year						
Shiffman (2009); <sup>91</sup> RCT, double-blind, parallel	To test the efficacy of nicotine gum in facilitating cessation through gradual reduction  Nicotine gum could be used to facilitate smoking reduction and cessation	US; multicentre (27 sites); Glaxo-SmithKline	Use gum as needed to reduce smoking; 6 months	Nicotine gum vs. placebo	Treatment: Patients chose dose of gum (as they would in an over-the-counter setting) ; received active dosage of their choosing (2-mg or 4-mg nicotine) or placebo gum; 12 wks treatment: 1 piece every 1-2 h for the first 6 wks; 1 piece every 2-4 h for the next 3 wks; and then 1 piece every 4-8 h for a final 3 wks.  No instruction, counselling, or intervention was provided. Participants were then allowed to use gum “as needed to stay smoke-free” for an additional 12 wks Follow-up: 6 months	Self-reported abstinence, verified by CO levels $\leq 10$ ppm CAR at 6 months	3,297 / NR / 211
Tonnesen (1988); <sup>98</sup> RCT, double-blind, parallel	To study the effectiveness of nicotine gum in combination with group counselling in smoking cessation	Denmark (1 site); Government; A B Leo supplied gum	4 months; 2 years	Nicotine gum (2 mg) vs. placebo (for low-dependent smoking)  Nicotine gum	Treatment: 4 months treatment; high-dependent smokers: 4 mg first for 6 wks, then 2 mg, or 2 mg nicotine for the entire period; low-dependent smokers: 2 mg nicotine or	Self-reported abstinence, verified by CO levels $< 6$ ppm	173 / NR / 171

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	The efficacy of nicotine gum related to dose and not due to placebo effect			(2 mg) vs (4 mg) (for high-dependent smoking)	placebo All received 6 group counselling sessions during the first 4 months, led by a physician Follow-up visits: 6 wks, then 3, 6, 9, 12, and 24 months		
Wennike (2003); <sup>97</sup> RCT, double-blind, parallel	To test the effect of nicotine gum and placebo in smokers not motivated or not able to quit smoking  Nicotine gum promoted cessation in population of smokers unwilling to quit	Sweden (No. of sites NR); Pharmacia AB	12 months; 2 years	Nicotine gum vs. placebo	Treatment: active (2 or 4 mg nicotine gum) or placebo; use ad lib up to 1 year; 4-mg gum for high-dependent smokers and 2-mg gum for low-dependent smokers; each group had placebo control Follow-up visits: wks 2, 6, and 10, and months 4, 6, 9, 12, and 24 All received moderate behavioural smoking reduction information, general implications of smoking and effects on health	Self-reported abstinence, verified by CO levels <10 ppm	411 / 169 (41.1%) / 153 (37.2%)
<b>Nicotine lozenge vs. placebo</b>							
Shiffman (2002, 2005); <sup>104,363,383</sup> RCT, double-blind, parallel	To test the safety and efficacy of a new nicotine polacrilex lozenge for smoking cessation	UK; multicentre (4 sites), US (11 sites); GlaxoSmithKline Consumer Healthcare	Up to 24 wks; 52 wks	Nicotine lozenge vs. placebo	Treatment: 4-mg nicotine lozenge to participants who reported smoking within 30 min of waking, 2-mg for the others; one lozenge every 1-2 hrs,	Self-reported abstinence, verified by CO levels ≤10 ppm CAR at wks 6,	1818 / 370 (20.4%) / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	Nicotine lozenge was a safe and effective treatment for smoking cessation				with minimum 9/d for 6 wks, then recommended tapering to wk 24 Follow-up visits: wks 2, 4, 6, 12, 24 and 52	12, 24, 52	
<b>Nicotine sublingual vs. placebo</b>							
Glover (2002); <sup>105</sup> RCT, double-blind, parallel	To assess the efficacy and safety of a nicotine sublingual tablet in smoking cessation  Nicotine sublingual tablet was effective as smoking cessation aid	US (1 site); Pharmacia & Upjohn	6 months (3 months treatment, 3 months tapering); 12 months	Nicotine sublingual vs. placebo	Treatment: 2-mg nicotine or placebo tablet; low dependent smokers: 1 tablet/h up to 20 tablets/d; high dependent smokers: 2 tablets/h up to 40 tablets/d All received minimal individual psychological support (<10 min) at every follow-up visit after the quit date (brochure and answer questions) Follow-up visits: wks 1, 2, 3, 6 and months 3, 6, and 12	Self-reported abstinence, verified by CO levels <10 ppm CAR at end of wks 2 onward	241 / NR / NR
Tonnesen (2006); <sup>106</sup> RCT, double-blind, parallel	To evaluate the efficacy of nicotine sublingual tablets and two levels of support for smoking cessation in COPD patients	Denmark; multicentre (7 sites); Government and Pfizer	12 weeks to 12 months; 12months	Nicotine sublingual vs. placebo  Low support vs. high support	Treatment: 12 wks of active (2 mg) or placebo tablets, with a possibility of continued use up to 12 months; 1- 2 tablets/h Low-support: 4 visits and 6 telephone calls High support: 7 visits and 5 telephone calls	Self-reported abstinence, verified by CO levels <10 ppm	370 / NR / 114 (30.8%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	Nicotine sublingual tablet was effective as smoking cessation aid in patients with COPD				All visits were on an individual basis and were conducted by nurses (20-30 min); each telephone call (10 min); total contact time was 2.5 h for low-support and 4.5 h for high-support groups At each visit, all received counselling on smoking cessation and a take-home booklet		
Wallstrom (2000); <sup>107</sup> RCT, double-blind, parallel	To evaluate the efficacy and safety of a 2-mg nicotine sublingual tablet in smoking cessation  Nicotine sublingual tablet increased smoking cessation rate and reduced craving compared to placebo	Sweden (1 site); Pharmacia & Upjohn	3 months treatment; up to 6 months tapering; 12 months	Nicotine sublingual vs. placebo	Treatment: 2mg or 4 mg nicotine or placebo tablets; low dependent smokers: 1-2 tablets of 2 mg nicotine/h (max 20 tablets/d); highly dependent smokers: 2 tablets of 4 mg nicotine/h (max 40 tablets/d); 3 months of treatment, tapering up to 6 months Follow-up visits: wks 2, 3, and 6, and months 3, 6, and 12 All received booklet and brief counselling (5 min) on smoking cessation at each visit	Self-reported abstinence, verified by CO levels <10 ppm	247 / NR / NR

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<b>Oral nicotine inhaler vs. placebo</b>							
Bolliger (2000); <sup>108</sup> RCT, double-blind, parallel	To determine whether use of an oral nicotine inhaler can result in long term reduction in smoking and whether concomitant use of nicotine replacement and smoking is safe  Nicotine inhaler achieved sustained smoking reduction, but not cessation over two years	Switzerland; multicentre (2 sites); Pharmacia & Upjohn Consumer Healthcare	Up to 18 months; 24 months	Nicotine inhaler vs. placebo	Treatment: oral nicotine (4-5 mg per cartridge) inhaler or placebo; recommended dose: 6-12 cartridges over 24 h; participants were encouraged to decrease use after 4 months, but were permitted to use up to 18 months Follow-up visits: wks 1, 2, 3 and 6, and months 3, 4, 6, 12, 18 and 24 All received counselling on smoking reduction at each visit	Self-reported abstinence, verified by CO levels <10 ppm CAR and PP abstinence at 4, 12, and 24 months	400 / NR / 310 (77.5%)
Hjalmarson (1997); <sup>109</sup> RCT, double-blind, parallel	To assess the efficacy and safety of the nicotine inhaler as an aid in smoking cessation  Nicotine inhaler was an effective smoking cessation aid	Sweden (1 site); Pharmacia & Upjohn	6 months; 1 year	Nicotine inhaler vs. placebo	Treatment: oral nicotine (10 mg per cartridge) inhaler or placebo; use inhaler for 20-30 min and puff more frequently than when smoking; use the same one 3-4 times before switching to a new one; use on an ad lib basis, minimum 4 inhalers per day; participants were encouraged to decrease use after 3 months, but were permitted to use up	Self-reported abstinence, verified by CO and saliva cotinine (cut-off levels: NR) CAR from wks 2 to 12 months	247 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					to 6 months All received group behavioural support (8 times in 6 wks; each session lasted from 45-60 min) given by psychologists Follow-up visits: wks 2, 3 and months 3, 6, and 12		
Rennard (2006); <sup>110</sup> RCT, double-blind, parallel	To evaluate the efficacy of the nicotine inhaler in reducing smoking Nicotine inhaler was effective in smoking reduction and cessation	US; multicentre (3 sites); sponsor NR	Up to 12 months; 15 months	Nicotine inhaler vs. placebo	Treatment: oral nicotine (10 mg per cartridge) inhaler or placebo; use on ad lib basis; recommended dose of 6-12 cartridges/d, for up to 12 months; use max dose for the first 2 wks; smoking cessation was recommended from month 6; no support intervention Follow-up visits: wks 2, 6, and 10, and months 4, 6, 9, 12, and 16	Self-reported abstinence, verified by CO and plasma cotinine and thiocyanate (cut-off levels: NR) PP abstinence at 4, 12 and 15 months	429 / NR / 154 (35.9%)
Schneider (1996); <sup>111</sup> RCT, double-blind, parallel	To assess the efficacy and safety of a nicotine inhaler in smoking cessation Nicotine inhaler was useful for short term cessation	US (1 site); Pharmacia & Upjohn	3 months treatment and 3 months tapering; 12 months	Nicotine inhaler vs. placebo	Treatment: oral nicotine (5 mg per cartridge) inhaler or placebo; use on ad lib basis; use 4-20 cartridges/d; use each inhaler 5 times with 100 puffs per use; use up to 6 months; start weaning at 3 months	Self-reported abstinence, verified by CO levels of $\leq 8$ ppm and saliva cotinine levels of $\leq 14$ ng/ml CAR at each	223 / NR / NR

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					Follow-up visits: wks 2, 3, 6, and months 3, 6, and 12	time of follow-up, up to 1 year	
Tonnesen (1993); <sup>112</sup> RCT, double-blind, parallel	To evaluate the efficacy of a new nicotine inhaler system for smoking cessation  Nicotine inhaler was safe and increased success rates of smoking cessation attempts	Denmark (No. of sites NR); Kabi Pharmacia Therapeutics	3 months treatment and 3 months tapering; 52 wks	Nicotine inhaler vs. placebo	Treatment: oral nicotine (10 mg per cartridge) inhaler or placebo; use between 2 -10 inhalers per day ad lib; puff 10 times more often compared with smoking a cigarette; change to a new inhaler when feeling no more effect; 3 months treatment followed by 3 months tapering Follow-up visits: wks 2, 3, 6, 12, 24, and 52 All received 7-min video tape about smoking cessation at the first visit and 5-min introductory speech by physician at each visit	Self-reported abstinence, verified by CO levels <10 ppm CAR and PP abstinence at wks 6, months 3, 6, and 12	286 / NR / NR
<b>Nicotine nasal spray vs. placebo</b>							
Blondal (1997); <sup>113</sup> RCT, double-blind, parallel	To evaluate the therapeutic efficacy of nicotine nasal solution for smoking cessation  Nicotine nasal spray increased the	Iceland (1 site); Pharmacia & Upjohn	3 months or more (not more than 1 year); 2 years	Nicotine spray vs. placebo	Treatment: nasal spray containing 0.5 mg nicotine per 50 µL squirt or placebo; use on ad lib basis; max 5 doses/h (5 mg nicotine) and 40 doses/d (40 mg nicotine); 3 months treatment, but	Self-reported abstinence, verified by CO levels of ≤9 ppm CAR at months 3, 6, and year 1 and	157 / NR / NR

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	abstinence rate during the first 6 months after quitting day				could continue up to 1 year All received group behavioural support and booklet on smoking cessation Follow-up visits: months 3, 6, 12, and 24	years 2	
Hjalmarson (1994); <sup>114</sup> RCT, double-blind, parallel	To evaluate the efficacy and safety of nicotine nasal spray for smoking cessation Nicotine nasal spray in combination with group treatment was an effective aid to smoking cessation	Sweden (1 site); Kabi Pharmacia	3 months, but could use up to 1 year; 1 year	Nicotine spray vs. placebo	Treatment: nasal spray containing 0.5 mg nicotine per 50 µL spray or placebo; 1 dose = 2 sprays (1.0 mg nicotine); max 5 doses/h and 40 doses/d; 3 months treatment, but could continue up to 1 year All received group behavioural support (45-60 min) at each session (8 sessions over 6-wk period) Follow-up visits: months 3, 6, and 12	Self-reported abstinence, verified by CO levels of <10 ppm CAR at wks 2 and 6, and months 3, 6, and 12	248 / NR / NR
Schneider (1995); <sup>115</sup> RCT, double-blind, parallel	To test the safety and efficacy of nicotine nasal spray for smoking cessation Nicotine nasal spray was efficacious for	US (1 site); Pharmacia	Up to 6 months (tapering starting at months 3); 1 year	Nicotine spray vs. placebo	Treatment: nasal spray containing 0.5 mg nicotine per 50 µL spray or placebo; 1 dose = 2 sprays (1.0 mg nicotine); min 8 doses/d, no more than 32 doses/d for the first 6 wks; use up to 6 months	Self-reported abstinence, verified by CO levels of ≤8 ppm CAR and PP abstinence at all follow-up visits	255 / NR / NR

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	smoking cessation				All received a 7-min instruction video on how to use the spray and a booklet on smoking cessation Follow-up visits: wks 2, 3, 6 and months 3, 6 and 12		
Sutherland (1992); <sup>116</sup> RCT, double-blind, parallel	To assess the efficacy and safety of a nasal nicotine spray as an adjunct to group treatment for smoking cessation  Nicotine nasal spray combined with supportive group treatment is an effective aid to smoking cessation	UK (1 site); Government and Kabia Pharmacia	3 months or more; 12 months	Nicotine spray vs. placebo	Treatment: nasal spray containing 0.5 mg nicotine per 50 µl spray or placebo; 1 dose = 2 sprays (1.0 mg nicotine); max 5 doses/h and 40 doses/d; 3 months treatment, but could continue using beyond this time All received group behavioural support (45-60 min) at each session (6 sessions over 1-month period) Follow-up visits: months 2, 3, 6, 9, and 12	Self-reported abstinence, verified by CO levels of <10 ppm CAR and PP abstinence at all follow-up visits	227 / NR / NR
<b>Nicotine patch vs. nicotine spray</b>							
Croghan (2003); <sup>117</sup> RCT, open-label, parallel	To determine whether the combined use of nicotine patch therapy and nicotine nasal	US; multicentre (No. of sites NR); Government	6 wks; 6 months	Nicotine patch vs. nicotine spray vs. patch + spray	Three treatment arms: 1. 15-mg patch for 16 h/d, new patch each morning 2. nicotine nasal spray (0.5 mg per spray),	Self-reported abstinence, verified by CO levels of <8 ppm 7-day PP	1384 / 738 (53.3%) / 415 (30%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	<p>spray would improve smoking abstinence rates compared to either treatment alone</p> <p>There was no difference between nicotine spray and nicotine patch in smoking cessation</p>				<p>max 2 sprays at 5 doses/h or 40 doses/d</p> <p>3. Combination of patch and spray</p> <p>Each treatment was initiated within 7 days of randomization and was to be continued for 6 wks</p> <p>Follow-up visits: 3 wks, 6 wks (end of treatment), and 6 months (end of study)</p>	<p>abstinence at 3 wks, 6 wks and 6 months</p>	
Lerman (2004); <sup>118</sup> RCT, open-label, parallel	<p>To evaluate the comparative efficacy of transdermal nicotine and nicotine nasal spray and identify predictors of treatment outcome</p> <p>Abstinence rates for the nicotine patch and nicotine spray were not significantly different at 6-month follow-up</p>	US; multicentre (2 sites); Government, Pharmacia & Upjohn provided nicotine nasal spray, GlaxoSmithKline provided nicotine patch	8 wks; 6 months	Nicotine patch vs. nicotine spray	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>1. Patch: 8-wk treatment period; 24-h tapering dose formulation: 4 wks at 21 mg, 2 wks at 14 mg and 2 wks at 7 mg</li> <li>2. Spray: 8-wk treatment period; 1.0 mg dose (0.5-mg spray in each nostril); 8-40 times /d (max 5 doses/h), with tapering by one-third for 2 wks after 4 wks of use, then taper again after the 2wks</li> </ol> <p>All received 7 sessions of</p>	<p>Self-reported abstinence, verified by CO levels of &lt;10 ppm</p> <p>CAR, PAR and PP</p> <p>abstinence at 8 wks and 6 months</p>	299 / NR / 249 (83.3%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					group behavioural counselling TQD: wk 3 Follow-up: 8 wks (end of treatment) and 6 months (end of study)		
<b>Nicotine patch vs. nicotine gum vs. placebo</b>							
Moolchan (2005); <sup>119</sup> RCT, double-blind, double-dummy, parallel	To determine the safety and efficacy of a nicotine patch and gum for adolescents who want to quit smoking  There was no significant effect of patch versus gum or gum versus placebo on the cessation outcomes. Nicotine patch was effective compared with placebo	US (No. of sites NR); Government	12 wks; 6 months	Nicotine patch vs. nicotine gum vs. placebo	Three treatment arms: 1. Active patch and placebo gum: 14-mg or 21-mg nicotine patch 2. Active gum and placebo patch: 2 mg or 4 mg nicotine gum; use as needed 3. Placebo gum and placebo patch All received brief individual counselling (3-4 min) on the medication side effects and 45 min cognitive-behaviour group therapy at each treatment visit All were compensated with \$90 for the baseline assessment and \$135 after study completion	Self-reported abstinence, verified by CO levels of $\leq 6$ ppm 7-day PP abstinence at 1 week, 12 weeks and 6 months	120 / NR / 53 (44.2%)
<b>Nicotine lozenge vs. nicotine gum</b>							
Pack (2008); <sup>120</sup>	To compare the efficacy of	US (1 site); Government	8 wks; 1 year	Nicotine lozenge vs.	Participants were randomized to either	Self-reported abstinence,	408 / 270 (66.2%) /

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
RCT, parallel	nicotine lozenge and gum for smoking cessation  Nicotine lozenge and nicotine gum appeared to be equally effective			nicotine gum Quit line vs. self-help brochure	lozenge or gum, and to either Quit Line or self help. Treatment: 8 wks of NRT Follow-up: 8 wks, 6 months, and 1 year Tobacco Quit Line group: 3 follow-up calls within 30 days of the TQD Self help: received brochure on smoking cessation	verified by CO levels of <10 ppm 7-day PP abstinence at 8 weeks, 6 months and 1 year	285 (69.9%)
<b>Nicotine patch vs. nicotine inhaler</b>							
Tønnesen (2000); <sup>121</sup> RCT, open-label, parallel	To compare the effect on smoking cessation with nicotine replacement in a lung clinic in a low-resource set-up  No difference in success rates between nicotine patch and inhaler was observed	Denmark (No. of sites NR); Pharmacia & Upjohn	Up to 9 months; 12 months	Nicotine patch (5 mg or 15 mg) vs. nicotine inhaler vs. patch (15 mg) + inhaler	Four treatment arms: 1. 5-mg nicotine patch 2. 15-mg nicotine patch 3. nicotine inhaler 4. 15-mg nicotine patch + inhaler  NRT was recommended to be used up to 3 months, with the possibility of continuing use for up to 9 months on an individual basis TQD: wk 2 All received brief counselling from nurses Follow-up visits: wks 2 and 6, and months 3, 6, 9, and 12	Self-reported abstinence, verified by CO levels of <10 ppm CAR, PAR and PP abstinence at each follow-up visit	446 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
<b>Nicotine mouth spray vs. nicotine gum vs. oral nicotine inhaler</b>							
Bolliger (2007); <sup>122</sup> RCT, open-label, parallel	To test the preference, efficacy and, safety of nicotine mouth spray compared with nicotine gum and oral inhaler  There was no significant difference between groups in the efficacy of pharmacotherapies.	South Africa (No. of sites NR); NicoNovum AB	12 wks; 26 wks	Mouth spray vs. gum vs. oral inhaler	Three treatment arms: 1. Mouth spray (1 mg/actuation), taken one spray at a time; recommended 6-12 actuations/d 2. Nicotine gum (2 mg): use ad lib, recommended 6-12/d 3. Inhaler (10 mg/blister): use ad lib; recommended 6-12 cartridges/d Follow-up visits: wks 4, 8, 12, and 26	Self-reported abstinence, verified by CO levels of <10 ppm CAR at 26 wks	100 / NR / NR
<b>Nicotine patch vs. nicotine patch + behaviour support</b>							
Alterman (2001); <sup>123</sup> RCT, parallel	To study the efficacy of 3 levels of medical-behavioural treatment intensity in conjunction with NRT  Group differences were statistically significant at both short and long-term	US (No. of sites NR); Government	8 wks; 52 wks	Nicotine patch + low intensity vs. patch + middle intensity vs. patch + high intensity	Three treatment arms: 1. Low intensity: patch + 1 advice and education (A&E) session (15-20 min) 2. Middle intensity: patch + 4 A&E sessions 3. High intensity: patch + 4 A&E sessions + 12 wks individualized cognitive behavioural therapy (45-50 min)	Self-reported abstinence, verified by CO levels of $\leq 9$ ppm or urine cotinine levels <50 ng/ml (GC/MS) or <200 ng/ml (ELISA)	240 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					Nicotine patch: 21 mg/d for 4 wks, 14 mg/d for 2 wks, then 7 mg/d for 2 wks Follow-up visits: wks 3, 6, 9, 26, and 52		
Bock (2008); <sup>124</sup> RCT, parallel	To examine the efficacy of a smoking cessation intervention on abstinence rates and motivation to quit smoking  Abstinence rates were significantly greater among participants receiving the tailored intervention compared with those given usual care. The differences decreased over time	US; hospital emergency department (1 site); Government	8 wks; 6 months	Nicotine patch + usual care vs. nicotine patch + behaviour counselling and telephone follow-up	Two treatment arms: 1. patch + usual care 2. patch + one behaviour counselling session (30-min) + two brief telephone follow-up (<15 min) at wks 2 and 4  All received brief (<10 min) telephone counselling on their quit day and again 7 days later Follow-up assessments: 1, 3, and 6 months	Self-reported abstinence, verified by cotinine levels of $\leq 15$ ng/ml 7-day PP abstinence at 6 months	543 / NR / 292 (53.8%)
Lando (1997); <sup>125</sup> RCT, parallel	To assess telephone support as an adjunct to a managed care-based, single-session group	US (No. of sites NR); Lederle Laboratories	Up to 8 wks; 12 months	Nicotine patch vs. patch + Help Line vs. patch + help line + telephone	Three treatment arms: 1. patch 2. patch + Help Line 3. patch + Help Line + telephone counselling (4 calls	Self-reported abstinence, verified by CO levels (cut-off: NR) CAR and PP	509 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	orientation smoking cessation program with nicotine patch therapy  There was no evidence of benefit from telephone support beyond the initial physician-led group orientation session			counselling	at wks 1, 4, 7-9, and 12) All received orientation session (90 min) Follow-up: wks 2, 5, 8, and 12, and months 6 and 12	abstinence at 6 and 12 months	
Lifrak (1997); <sup>126</sup> RCT, parallel	To study the effect of intense behavioural support and brief advice as an adjunct to nicotine patch therapy for smoking cessation  The abstinence rates at follow-up points were comparable for the two treatment groups	US (1 site); sponsor NR	8 wks; 52 wks	Nicotine patch + moderate intensity (MI) brief advice vs. patch + high intensity (HI) behavioural counselling	Two treatment arms: 1. Patch + MI (4 smoking cessation sessions with a nurse-practitioner giving advice and instruction) 2. Patch + HI (16 weekly individual cognitive/behavioural relapse-prevention therapy sessions) Nicotine patch: 21 mg/d for 6 wks, 14 mg/d for next 2 wks, and 7 mg/d for the last 2 wks Follow-up: wks 9, 16, 26, and 52	Self-reported abstinence, verified by CO levels of <10 ppm or urine cotinine levels <200 ng/ml 7-day PP abstinence at wks 9, 16, 26, and 52	69 / 43 (62.3%) / NR
Simon (2003); <sup>127</sup>	To determine whether intensive	US (1 site); Government	8 wks; 52 wks	Nicotine patch + minimal	Two treatment arms: 1. Patch + minimal	Self-reported abstinence at	223 / NR / 202

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
RCT, parallel	<p>cognitive-behavioural intervention begun during hospitalization, when combined with transdermal NRT, is more effective than a minimal counselling intervention combined with transdermal NRT in helping inpatients to quit smoking</p> <p>Significant differences between groups were observed with self-reported abstinence, but not with biochemical confirmed abstinence</p>			counselling vs. patch + intense counselling	<p>counselling (on danger of smoking and benefit of quitting)</p> <p>2. Patch + intense counselling (intense cognitive behavioural intervention on the nearest weekday before discharge in a session lasting 30-60 min)</p> <p>All received self-help booklet and 2-month supply of patches (dosage NR) at discharge; dose was based on the number of cigarettes smoked</p> <p>Follow-up: by telephone at 6 and 12 months</p>	<p>12 months, verified by saliva cotinine levels &lt;15 ng/ml</p> <p>7-day PP abstinence at wks 52</p>	
Solomon (2000); <sup>128</sup> RCT, parallel	To test the impact of free nicotine patches plus proactive telephone peer support to help	US (No. of sites NR); Government; patches supplied by SmithKline Beecham	Up to 3 months; 6 months	Patch vs. patch + telephone support	Two treatment arms: 1. Patch only 2. Patch + proactive telephone support (provided by women ex-smokers who had	Self-reported abstinence, verified by CO levels of ≤8 ppm 7-day PP	214 / 193 (90.2%) / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	<p>low-income women stop smoking</p> <p>The significant differences between groups were found in the 3-month, but not in the 6-month follow-up</p>				<p>received 7 h training); call was given on a weekly to bi-weekly basis for up to 3 months</p> <p>Nicotine patch: for history of &gt;10 cigarettes/d: 6 wks of 21-mg patches, 2 wks of 14-mg patches, and 2 wks of 7-mg patches; for history of 5-10 cigarettes/d: 6 wks of 14-mg patches, and 2 wks 7-mg patches</p> <p>Follow-up: 3 and 6 months</p>	abstinence at months 3 and 6	
Stein (2006); <sup>129</sup> RCT, parallel	<p>To test, in combination with the nicotine patch, the incremental efficacy of a maximal, tailored behavioural treatment over a minimal treatment for smoking cessation</p> <p>Smoking cessation rates in methadone-maintained smokers were low,</p>	US; clinics (5 sites); Government; GlaxoSmithKline provided patches	8 to 12 wks; 6 months	Patch + brief advice vs. patch + behavioural counselling	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>1. Patch + brief advice (self-help materials and ~3 min of quit smoking message for up to 2 visits)</li> <li>2. Patch + behavioural counselling (up to 3 visits): initial motivational interviewing session (30 min), session with the study interventionist on the quit date (15-30 min), and a follow-up session (15 min);</li> </ol>	Self-reported abstinence, verified by CO levels of <8 ppm 7-day PP abstinence at months 3 and 6	383 / 317 (82.8%) / 312 (81.5%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	and a tailored behavioural intervention did not increase quit rates over patch and minimal treatment				<p>participants could contact study staff throughout the study for any problems</p> <p>Nicotine patches: for history of &lt;2 packs/d: 8-wk protocol (21 mg for 4 wks, 14 mg for 2 wks, and 7 mg for 2 wks); for history of <math>\geq 2</math> packs/d: 12-wk protocol (42 mg for 4 wks, 35 mg for wks 5 and 6, 28 mg for wks 7 and 8, 21 mg for wks 9 and 10, 14 mg for wk 11, and 7 mg for wk 12</p> <p>Follow-up: 3 and 6 months</p>		
Wiggers (2006); <sup>130</sup> RCT, parallel	<p>To test the effect of minimal intervention strategy in addition to NRT to support smoking cessation in cardiovascular outpatients as compared with NRT alone</p> <p>No significance between groups were found</p>	The Netherlands (1 site); Government; Novartis provided patches	8 wks; 12 months	Patch alone vs. Patch + behavioural intervention	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>1. Patch alone (usual care only)</li> <li>2. Patch + behavioural intervention adapted for cardiology inpatients (15-30 min counselling session, 6 steps were performed by nurse practitioner); a second counselling session provided on patient's request</li> </ol> <p>Nicotine patches: 8-wk</p>	Self-reported abstinence, verified by urine and or saliva cotinine (cut-off levels: NR) 7-day PP abstinence at 12 months	385 / NR / 331 (86%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
					treatment (history of <20 cigarettes/d): 14 mg/24h; history of ≥20 cigarettes/d: 21mg/24h Follow-up: 12 months		
<b>Nicotine gum vs. nicotine gum + behaviour</b>							
Fortmann (1995); <sup>131</sup> RCT, parallel	To test the effect of self-help materials in nicotine gum therapy for smoking cessation  There was no significant main effect for the self-help materials, no interaction between gum and materials	US (No. of sites NR); Government	NR; 12 months	Nicotine gum vs. gum + self-help program vs. self-help program	Three treatment arms (selected out of 4): 1. Gum only 2. Gum + self-help prevention program (Phase 1: design own relapse prevention program emphasizing food, physical activity, and other replacement behaviours to combat craving; Phase 2: maintenance of new replacement behaviours and coping with relapse risks 3. Self-help program only Nicotine gum: one piece (2 mg)/h, minimum 10 pieces/d \$100 incentive for quitting for 6 months Follow-up: 6 and 12	Self-reported abstinence, verified by CO levels of <9 ppm and saliva cotinine levels of < 20 ng/ml 7-day PP abstinence at months 6 and 12	783 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
					months		
Ginsberg (1992); <sup>132</sup> RCT, parallel	To examine the effectiveness of 3 increments of psychological and social support to better understand the optimal level of support to supplement nicotine gum  No significance between groups were found	US (No. of sites NR); Government	NR; 52 wks	Nicotine gum vs. gum + psychological treatment vs. gum + psychological treatment and partner support	Three treatment arms: 1. Gum only 2. Gum + psychological treatment 3. Gum + psychological treatment and partner support  Treatment details: NR Follow-up: wks 4, 12, 26 and 52	Self-reported abstinence, verified by CO levels <10 ppm or by urine cotinine levels <50 ng/ml, or by urine thiocyanate <65 µmol/mg creatinine 7-day PP abstinence at all follow-up assessments	99 / NR / NR
Hall (1985); <sup>133</sup> RCT, parallel	To assess the efficacy of nicotine gum and behavioural treatment in smoking cessation  The differences between groups were significant at up to 26 weeks, but not at 52 weeks	US (No. of sites NR); Government	Up to 6 months; 52 wks	Nicotine gum vs. Nicotine gum + behavioural treatment vs. behavioural treatment alone	Three treatment arms: 1. Nicotine gum: 2-mg, use up to 6 months; detail of treatment NR 2. Gum + behavioural treatment 3. Behavioural treatment  The behavioural treatment condition included 30-s aversive smoking of 3 cigarettes, relapse-prevention skill training, relaxation training, and written exercises to	Self-reported abstinence, verified by CO levels <10 ppm and blood thiocyanate levels <85 mg/ml PP abstinence at follow-ups	120 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					increase commitment; fourteen 75-min sessions over 8-wk period Follow-up assessment: wks 3, 12, 26, and 52		
Hall (1987); <sup>85</sup> RCT, parallel  (same study in gum vs. placebo)	To assess the efficacy of 2-mg nicotine gum and behavioural support in smoking cessation  Higher rates of abstinence were obtained from individuals receiving low contact condition plus gum	US (No. of sites NR); Government	NR; 1 year	Nicotine gum vs. placebo vs. Nicotine gum + behaviour vs. placebo + behaviour	Treatment: gum was available for 1 year from the beginning of treatment Participants were randomized to 4 arms: gum, placebo, gum + behavioural support, and placebo + behavioural support 14 sessions of behavioural support (75 min each)	Self-reported abstinence, verified by CO levels <8 ppm or serum thiocyanate levels <95 mg/ml)	139 / NR/ 128
Killen (1984); <sup>134</sup> RCT, parallel	To assess the efficacy of nicotine gum and self-regulation training in smoking relapse prevention  Skill training increased the efficacy of nicotine gum	US (No. of sites NR); Merrell-Dow Pharmaceuticals Inc.	7 wks; 12 months	Nicotine gum vs. gum + skill training vs. skill training alone	Three treatment arms: 1. Nicotine gum: 2-mg gum for 7 wks; use ad lib; reduce gum usage beginning wk 3 and no more gum after wk 7 2. Gum + skills training 3. Skills training Skills training: cognitive behavioural group training during wks 2 and 3; directed own	Self-reported abstinence, verified by CO levels <8 ppm or serum thiocyanate levels <100 µmol/L)	64 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
					maintenance program and received performance feedback in wks 4-7		
<b>NRT + behaviour vs. usual care</b>							
Baker (2006); <sup>135</sup> RCT, parallel	To compare an integrated psychological and NRT intervention for people with a psychotic disorder with routine care control  Nicotine patch plus motivational interview/cognitive behavioural therapy had higher abstinence rates than usual care among people with psychotic disorder	Australia; multicentre (2 sites); Government, GlaxoSmithKline provided nicotine patches	10 wks; 12 months	Nicotine patch + behaviour vs. usual care	Two treatment arms: 1. Nicotine patch + behavioural support: 8 individual 1-h sessions of motivational interviewing and cognitive behaviour therapy plus NRT (patch), in addition to usual care 2. Usual care: access to general practitioners and publically funded mental health teams  All received booklet on smoking cessation Follow-up: 3, 6, and 12 months	Self-reported abstinence, verified by expired CO levels <10 ppm CAR and pp abstinence at follow-up	298 / NR / 247 (82.9 %)
Lacasse (2008); <sup>141</sup> RCT, parallel	To determine whether a smoking cessation intervention of moderate intensity would increase the smoking cessation rate in hospitalized	Canada (1 site); sponsor NR	8 wks; 1 year	Nicotine patch + behaviour vs. usual care	Two treatment arms: 1. Patch + behaviour (education and psychological) support 2. Usual care Nicotine patch: 21-, 14-, 7-mg; dose determined by	Self-reported abstinence, verified by cotinine assay (cut-off level: NR) PP abstinence at 1 y	196 / NR / 171 (87.2%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	smokers  No significant differences between study groups were found				treating physician; treatment duration: 8 wks Education and psychological support: strong quit smoking message from treating physician, self-help motivational quitting or relapse prevention materials, brief cessation counselling, and follow-up support Usual care: no specific instruction of how to stop smoking; limited contact (6 month and 1 year follow-up only)		
Lewis (1998); <sup>66</sup> RCT, parallel	To assess the safety and efficacy of a treatment involving brief counselling and the nicotine patch among hospital inpatients  No significant differences between study groups were found	US (1 site); Elan Pharmaceutical Research Corporation	3 wks, 6 months	Nicotine patch + counselling vs. minimal care	Two treatment arms: 1. Nicotine patch (22 mg/d for wks 1-3 ) + counselling 2. Minimal care (brief physician-delivered motivational message to stop smoking)	Self reported abstinence, verified by CO levels $\leq 10$ ppm 7-day PP abstinence at 1, 3, and 6 wks , and 6 months	123 / NR / NR
Mohiuddin (2007); <sup>138</sup> RCT, parallel	To compare an intensive smoking cessation	US (1 site); sponsor NR	12 wks or more; 24 months	NRT and/or bupropion + behaviour vs.	All received counselling (~30 min) and self-help materials on smoking	Self-reported abstinence, verified by	209 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	<p>intervention against usual care in hospitalized high-risk smokers with acute cardiovascular disease</p> <p>Cessation rates were significantly greater in the intensive-treatment group compared to the usual-care group</p>			usual care	<p>cessation</p> <p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>NRT and/or bupropion + behavioural support</li> <li>Usual care</li> </ol> <p>Behavioural support: individual counselling (~60 min) on a weekly basis for minimum 3 months</p> <p>Follow-up visits: 3, 6, 12, and 24 months</p>	<p>expired CO (cut-off level: NR)</p> <p>CAR and PP abstinence at each visit</p>	
Molyneux (2003); <sup>142</sup> RCT, parallel	<p>To assess the efficacy of NRT plus counselling on smoking cessation in hospital inpatients</p> <p>NRT given with brief counselling to hospital inpatients in an effective routine smoking cessation intervention</p>	UK; hospital (1 site); Pharmacia	6 wks on NRT; 12 months	NRT + counselling vs. usual care	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>NRT + counselling</li> <li>Usual care</li> </ol> <p>Usual care: smoking status recorded, but no formal intervention</p> <p>Counselling: 20-min counselling by doctor or nurse on smoking cessation, advice leaflet</p> <p>NRT: 6 wk course of NRT, nicotine patch (15 mg, 16 h), nicotine gum (2 or 4 mg), nicotine inhaler (10 mg), nicotine sublingual tablet (2 mg), nicotine nasal spray (0.5 mg/spray)</p>	<p>Self-reported abstinence, verified by expired CO levels &lt;10 ppm</p> <p>PP abstinence and CAR at 3 and 12 months</p>	183 / 167 (91.3%) / 78 (42.6%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
					Follow-up: 3 and 12 months		
Nagle (2005); <sup>136</sup> RCT, parallel	To assess the efficacy of a brief nurse intervention for inpatients, with minimal follow-up post discharge, in achieving long-term smoking cessation among general hospital patients  Brief nurse-provided in-patient intervention did not significantly increase the smoking cessation rates compared with the control group	Australia (1 site); Government	NR; 12 months	NRT + nurse-provided intervention vs. usual care	Two treatment arms: 1. NRT (not specified) + nurse-provided intervention 2. Usual care Nurse-provided intervention: two brief counselling sessions about withdrawal symptoms, information booklets, and discharge letter to patients' general practitioners Usual care: no standardized smoking assessment, minimal contact about smoking or symptoms, no pharmacotherapy available, no discharge plan, and smoking behaviour was not considered part of counsellor's role	Self-reported abstinence, verified by expired CO levels <10 ppm and saliva cotinine levels <50 nmol/L 7-day PP abstinence at 12 months	1422 / NR / NR
Reid (2008); <sup>139</sup> RCT, parallel	To assess the efficacy of smoking cessation counselling as an adjunct to substance abuse	US; multicentre (7 sites); Government	8 wks patch, 9 wks counselling; 26 wks	Nicotine patch + counselling vs. usual care	Two treatment arms: 1. Nicotine patch + usual care + counselling 2. Usual care Patch: 21 mg/d for wks 1-	Self-reported abstinence, verified by expired CO levels ≤10 ppm	225 / NR / 210 (93.3%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	treatment-as-usual  Smoking cessation treatment increased cessation rates				6, and 14 mg/d for wks 7 and 8 Counselling: group, mood management, cognitive-behavioural therapy tailored for substance abuse; 9 sessions Follow-up visits: wks 13 and 26	7-day PP abstinence at wks 13 and 26	
Rodríguez-Artalejo (2003); <sup>143</sup> RCT, parallel	To assess the effectiveness of a smoking cessation intervention (minimal structured counselling and nicotine patch) at the work place  The intervention group achieved higher cessation rates than the control group	Spain; multicentre (3 sites); Novartis and Government	3 months; 12 months	Nicotine patch + counselling vs. control	Two treatment arms: 1. Nicotine patch + counselling 2. Control Nicotine patch: 3-month treatment regimes according the nicotine dependence levels Counselling: given by occupational health physician; a short session (5-8 min) of structured individualized counselling; brochure on smoking cessation; further 3 contacts with smokers [short counselling (2-3 min)] Control: short (30 s to 1 min) sporadic sessions of unstructured medical antismoking advice during medical check up Follow-up visits: days 2	Self-reported abstinence, verified by expired CO levels $\leq 10$ ppm CAR at follow-up visits	217 / 217 / 217

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					and 15, and months 3 and 12		
Simon (1997); <sup>140</sup> RCT, parallel	To determine whether a multicomponent smoking cessation intervention, administered during the perioperative period, could increase long term quit rates among smokers admitted for non-cardiac surgery  The intervention group achieved higher cessation rates than the control group	US (1 site); Government; Mario-Merrell Dow Inc provided nicotine gum and patch; Ciba-Geigy Corp provided nicotine patches	3 months; 12 months	Nicotine gum or patch + behaviour vs. control	Two treatment arms: 1. NRT + behavioural self-management techniques 2. Control Behavioural self-management: face-to-face in-hospital counselling, viewing a smoking cessation video tape, self-help literature, 3 months of telephone follow-up NRT: 3-month prescription for nicotine gum or patch, with instructions on their use Control: brief counselling on the dangers of smoking and the benefit of quitting, and self-help brochures	Self-reported abstinence, verified by serum or saliva cotinine levels <15 ng/ml PP abstinence at 12 months	324 / NR / NR
Wakefield (2004); <sup>137</sup> RCT, parallel	To determine whether a motivational interviewing intervention increased successful smoking cessation attempts of patients with cancer as	Australia (1 site); Government	3 months; 6 months	NRT (nicotine patch) + counselling vs. control	Two treatment arms: 1. NRT + counselling 2. Usual care NRT: given to patients with cigarette consumption of $\geq 15/d$ ; details, NR Counselling: specific advice and booklets about the benefits of quitting for	Self-reported abstinence, verified by expired CO levels <8 ppm 7-day PP abstinence at 6 months	137 / NR / 88 (64.2%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	<p>compared with usual care</p> <p>No difference in cessation rates between groups was observed</p>				<p>patients with cancer; telephone and in-person counselling using the framework of motivational interview</p> <p>Control: brief advice to quit, brochures and information about quit-line service</p> <p>Follow-up: 3 and 6 months</p>		
<b>NRT + behaviour vs. behaviour</b>							
Cinciripini (1996); <sup>145</sup> RCT, parallel	<p>To assess the process and outcome of combined nicotine replacement-behavioural therapy on smoking cessation</p> <p>The differences between groups decreased with time</p>	US (1 site); Government, Ciba Geigy Corporation and Marion Merrell Dow	9 wks of behaviour therapy and 12 wks NRT; 12 months	Nicotine patch + behaviour vs. behaviour alone	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>1. Patch + behaviour</li> <li>2. Behaviour alone</li> </ol> <p>Behaviour therapy: physiological and psychological effects of nicotine; deep breathing; use of behaviours incompatible with smoking; changing the environment in response to smoking urge</p> <p>NRT: begin using patch in wk 5; dose titration schedule using 24-, 14-, and 7-mg patches for total of 12 wks</p>	Self-reported abstinence, verified by expired CO levels <6 ppm 7-day PP abstinence at 1, 3, 6, and 12 months	64 / NR / NR
Gilbert (1989); <sup>154</sup> RCT, parallel	To compare the effect of (1) advice to quit, setting of a	Canada; primary care (9 sites); US government	2-3 months with gum; 1 year	Nicotine gum + intervention support vs.	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>1. Gum + intervention support</li> </ol>	Self-reported abstinence, verified by	223 / 206 (92.3%) / 204 (91.5%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	<p>quit date, self-help materials, and supportive follow-up visits of one group with (2) the same manoeuvre plus the offer of a prescription of nicotine gum (support plus gum)</p> <p>There was no evidence that nicotine gum enhanced cessation rates when added to a comprehensive intervention offered in primary care</p>			intervention support	<p>2. Intervention support alone</p> <p>Intervention support: physician's advice to quit smoking, setting a quit date, self-help materials, and supportive follow-up visit</p> <p>Gum: 2-mg nicotine gum, patients pay for the gum, stay on gum for 2-3 months</p> <p>All received follow-up visits at 1 week, 1 month, 2 months, and 1 year</p>	<p>saliva cotinine levels <math>\leq 10</math> ng/mL or saliva thiocyanate levels of <math>&lt; 100</math> ng/mL</p> <p>7-day PP abstinence at 1 year</p>	
Hand (2002); <sup>155</sup> RCT, parallel	<p>To compare the effect of NRT plus advice support with advice support alone in hospital patients, for smoking cessation</p> <p>NRT did not add to the smoking cessation rate achieved at 1 year</p>	UK (No. of sites NR); author's endowment fund	3 weeks NRT and 4 weeks advice & support; 1 year	NRT + advice & support vs. advice & support alone	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>1. NRT (patch + inhaler) + advice &amp; support</li> <li>2. Advice &amp; support alone</li> </ol> <p>Advice &amp; support: Counselling program (4 weekly sessions, each lasting 15-30 min)</p> <p>NRT: 3 weeks of combination of nicotine patches and inhaler (on</p>	Self-reported abstinence, verified by expired CO levels $< 10$ ppm	245 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	by regular advice and support				demand); up to 14 refills a week Quit date: within 7 days of the first visit Follow-up visits: 1 week after quit date, months 1, 2, 3, 6, and 12		
Harackiewicz (1988); <sup>146</sup> RCT, parallel	To evaluate the effectiveness of nicotine chewing gum in smoking cessation, when incorporated into a behaviourally oriented self-help program  No long-term effect of nicotine gum was observed	US; multicentre (2 sites); Merrell Dow	6 months on gum; 12 months	Nicotine gum + self-help manual vs. self-help manual vs. short booklet	Three treatment arms: 1. Nicotine gum + self-help manual 2. Self-help manual only 3. Short booklet only All received doctor or nurse advice to stop smoking Instructions were given on the use and side effects of nicotine gum; supplies of gum were freely dispensed for 6 months Follow-up visits: 6 weeks after the initial interview, then 3 follow-up visits at 3 month intervals	Self-reported abstinence, verified by expired CO <8 ppm and saliva thiocyanate <10 mg/dL CAR at all follow-up visits	197 / NR / 175 (88.8%)
Hill (1993); <sup>147</sup> RCT, parallel	To compare behaviour training only with behaviour training and nicotine gum for smoking cessation	US (No. of sites NR); Public funding; Merrell Dow supplied the nicotine gum	3 months; 12 months	Nicotine gum + behaviour vs. behaviour	Two treatment arms: 1. Nicotine gum + behaviour training 2. Behaviour training alone Behaviour training: information on health consequences of smoking,	Self-reported abstinence, verified by expired CO levels <10 ppm PP abstinence at 7 and 12	44 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	No difference between groups was observed				documentation of quitting smoking and quality of life, help to remove smoking related cues, set quit date, relapse prevention training, coping responses, problem-solving individual slips Nicotine gum: provided at no cost for 3 months, and available for up to 4 months	months	
Martin (1997); <sup>148</sup> RCT, parallel	To evaluate the effectiveness of 3 smoking interventions in non-hospitalized recovering alcoholics  No difference between groups was observed in 6-month and 1-year follow-up	US (1 site); Government	3-6 months on gum; 12 months	Nicotine gum + behaviour vs. behaviour + physical exercise vs. Behaviour	Three treatment arms: 1. Nicotine gum + behaviour counselling 2. Behaviour counselling + exercise 3. Behaviour Behaviour: 20-day quit program in combination with meetings and counselling intervention. Four weekly 60- to 75-min group sessions, followed by maintenance sessions. Behavioural components included self monitoring, relaxation, urge control instruction, relapse prevention and	Self-reported abstinence, verified by expired CO levels <10 ppm PP abstinence at 6 and 12 months	205 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
					quit contracts. TQD at wks 4 Physical exercise: in wk 8, on-site moderate-to-brisk walking (15-45 min); thrice weekly home exercise Gum: 2-mg nicotine gum, 1-6 pieces/d, use from 3 to 6 months		
Molyneux (2003); <sup>142</sup> RCT, parallel	To assess the efficacy of NRT plus counselling on smoking cessation in hospital inpatients  NRT given with brief counselling to hospital inpatients was an effective routine smoking cessation intervention	UK; hospital (1 site); Pharmacia	6 wks on NRT; 12 months	NRT + counselling vs. counselling	Two treatment arms: 1. NRT + counselling 2. Counselling alone Counselling alone: 20-min counselling by doctor or nurse on smoking cessation, advice leaflet NRT: 6 wk course of NRT, nicotine patch (15 mg, 16 h), nicotine gum (2 or 4 mg), nicotine inhaler (10 mg), nicotine sublingual tablet (2 mg), nicotine nasal spray (0.5 mg/spray) Follow-up: 3 and 12 months	Self-reported abstinence, verified by expired CO levels <10 ppm PP abstinence and CAR at 3 and 12 months	182 / 170 (93.4%) (at discharge) / 74 (40.7%)
Niaura (1994); <sup>149</sup> RCT, parallel	To investigate the effect of matching smokers to NRT (nicotine gum) on the basis of the pre-treatment level	US; community physicians (24 sites); Government	Gum use up to 4 months, counselling for 5 wks; 12 months	Nicotine gum + counselling vs. counselling	Four treatment arms (high and low nicotine dependence): 1. Nicotine gum + counselling (low dependence)	Self-reported abstinence, verified by expired CO levels ≤8 ppm or saliva	173 / NR / 150 (86.7%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	of nicotine dependence  No difference between groups was observed				2. Nicotine gum + counselling (high dependence) 3. Counselling (low dependence) 4. Counselling (high dependence) Counselling: 4 brief (15 min) individual sessions given by psychiatrist or psychologist to review smoking history, introduce self-help materials and treatment protocol, set quit date, improve solving problem skills, prevent relapse; treatment spanned a period of 5 wks Gum: 2-mg nicotine gum, 8-12 pieces/d; use gum at least 1 month and up to 4 months; patients pay for the gum	cotinine levels <20 ng/mL 7-day PP abstinence at 6 and 12 months	
Niaura (1999); <sup>150</sup> RCT, parallel	To test the efficacy of cue exposure treatment for smoking relapse prevention as an adjunct to current standard cognitive behavioural and pharmacological	US; outpatient behavioural medicine clinic (1 site); Government	NR; 12 months	Nicotine gum + behaviour vs. behaviour	Four treatment arms: 1. Behaviour + cue exposure + gum 2. Behaviour + cue exposure 3. Behaviour + gum 4. Brief behaviour Behaviour: coping skills, identifying high risk	Self-reported abstinence, verified by expired CO levels <8 ppm 7-day PP abstinence at 1, 3, 6, and 12 months	129 / 126 (98%) / 103 (80%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	treatment  No difference between groups was observed				situations, abstinence violation effect, coping with slips and relapses, life style management Gum: 2-mg nicotine gum; use ad lib Cue exposure: for breaking bond between smoking triggers and urges		
Okuyemi (2007); <sup>151</sup> RCT, parallel	To assess the efficacy of a motivational interview and nicotine gum for smoking cessation in low-income housing smokers  Nicotine gum plus educational materials were not effective for smoking cessation in low-income housing	US; public housing and section 8 developments (20 sites); sponsor NR	8 wks; 6 months	Nicotine gum + motivational interview vs. motivational interview	Two treatment arms: 1. Nicotine gum + motivational interview 2. Motivational interview Gum: 4-mg nicotine gum, 8-wk supply, instructions for using gum, and educational materials on quitting smoking Motivational interview: Counselling	Self-reported abstinence, verified by expired CO levels $\leq 10$ ppm or saliva cotinine levels $\leq 20$ ng/mL 7-day PP abstinence at 8 wks and 6 months	173 / NR / NR
Pirie (1992); <sup>152</sup> RCT, parallel	To assess the smoking cessation efficacy of the weight control strategy (behaviour weight control program) and	US (No. of sites NR); Government	NR; 12 months	FFS vs. Gum + FFS vs. behaviour + FFS vs. Gum + FFS + behaviour	Four treatment arms: 1. FFS program: 8 wks (orientation meeting + 7 treatment sessions); social support and	Self-reported abstinence, verified by expired CO and saliva cotinine and thiocyanate	417 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	<p>nicotine gum in addition to the American Lung Association's Freedom from Smoking (FFS) clinic program</p> <p>The added weight control program did not reduce smoking cessation rates</p>				<p>development of cognitive behavioural skills; TQD: 4<sup>th</sup> wk</p> <ol style="list-style-type: none"> <li>2. Gum (2-mg strength) + FFS</li> <li>3. FFS + behaviour weight control program (help avoid weight gain, counselling; recommend decrease caloric intake; exercise)</li> <li>4. Gum + FFS + behaviour</li> </ol> <p>Follow-up: 6 and 12 months</p>	(cut-off levels: NR) CAR and PP abstinence at 6 and 12 months	
Pollak (2007); <sup>153</sup> RCT, parallel	<p>To examine whether adding NRT to cognitive behavioural therapy for pregnant smokers increases rates of smoking cessation</p> <p>The adding of NRT to cognitive behavioural therapy promote</p>	US; multicentre (14 sites); Government	6 wks; 3 months postpartum	NRT + behaviour vs. behaviour	<p>Two treatment arms:</p> <ol style="list-style-type: none"> <li>1. NRT + behaviour</li> <li>2. Behaviour</li> </ol> <p>Behaviour therapy: 6 one-on-one counselling sessions (five face-to-face and one via telephone) NRT: allow to choose patch, gum or lozenge; dose was based on the smoking level; for lozenge or gum, use a 2-</p>	Self-reported abstinence, verified by saliva cotinine (cut-off level NR) 7-day PP abstinence at 7 wks post-randomization, 38 wks of pregnancy and 3 months	181 / 130 (71.8%) / 115 (63.5%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	smoking cessation in pregnant women				mg piece for each cigarette smoked; use up to 6 wks	postpartum CAR at 3 months postpartum	
Richmond (1993); <sup>156</sup> RCT, parallel	To assess the efficacy of 3 smoking cessation interventions administered by general practitioners (GP)  No significant difference between groups was observed	Australia; 26 GPs (9 sites); Government; Glaxo provided the nicotine gum	3 months; 1 year	Nicotine gum + behaviour vs. behaviour vs. gum + GP advice	Three treatment arms: 1. Nicotine gum + behaviour 2. Behaviour 3. Nicotine gum + GP advice  Structural behaviour change: initial visit and 4 follow-up visits, use a daily diary, learn to reduce cigarette consumption, complete questionnaire, education on health effects and risks of smoking, discuss smoking pattern, social supports GP advice: initial visit and 2 follow-up visits, advice from GP on health effects and risks of smoking Gum: nicotine gum, instruction booklet, use gum for about 3 months Follow-up visits: 3, 6 and 12 months	Self-reported abstinence, verified by expired CO levels <14 ppm CAR and PP abstinence at wks 1, 3 and months 3, 6, and 12	450 / NR / 318 (70.7%)
Segnan (1991); <sup>157</sup>	To examine the effectiveness of	Italy; 44 GPs (No. of sites NR); Government; Serono	3 months on gum; 1 year	Nicotine gum + counselling vs.	Two treatment arms (selected out of four):	Self-reported abstinence,	569 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
RCT, parallel	different practice-based approaches to assist patients of primary care physicians (GPs) to quit smoking and sustain cessation  No significant difference between groups was observed	SPA provided gum		counselling	1. Nicotine gum + counselling 2. Counselling Counselling: repeated one-on-one counselling on recruited day and at months 1, 3, 6, and 9; telephone follow-up Gum: nicotine gum provided to be used up to 3 months	verified by urine cotinine levels <100 ng/mg 7-day PP abstinence at 6 and 12 months	
<b>NRT doses</b>							
Jorenby (1995); <sup>384</sup> RCT, double-blind, parallel	To compare the efficacy and safety of 22-mg and 44-mg doses of transdermal nicotine therapy when it is paired with minimal, individual, or group counselling to improve smoking cessation rates  Higher-dose (44-mg) nicotine patch is not indicated for general clinical populations	US; multicentre (2 sites); Elan Pharmaceutical Research Corporation	8 wks; 26 wks	22-mg patch vs. 44-mg patch Counselling: minimal vs. individual vs. group	Six treatment arms: 1. 22-mg + minimal counselling 2. 22-mg + individual counselling 3. 22-mg + group counselling 4. 44-mg + minimal counselling 5. 44-mg + individual counselling 6. 44-mg + group counselling  Minimal: self-help pamphlet, minimal	Self-reported abstinence, verified by expired CO levels <10 ppm 7-day PP abstinence at wks 4, 8, and 26	504 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					<p>counselling with research staff (8 weekly visits)            Individual: self-help pamphlet, motivational message by physician, follow-up letter, individual counselling, meet briefly (&lt;15 min) with a nurse to assess progress at wks 1, 2, 4 after quit dates, get help to identify high risks and problem solving            Group: same as individual, 1 h group counselling session weekly for 8 wks</p>		
Killen (1999); <sup>385</sup> RCT, parallel	<p>To determine whether high dose nicotine patch therapy benefits heavy smokers</p> <p>Routine use of higher dose nicotine patch therapy is not indicated in treatment of nicotine dependence</p>	US (No. of sites NR); Government; Pharmacia and Upjohn AB (Sweden) provided nicotine patches	6 wks; 12 months	15-mg patch vs. 25-mg patch	<p>Treatment: 6 wks with no tapering period, 15 or 25 mg nicotine patch delivered over 16 h. All received self-help treatment booklet            Follow-up: 2, 6, and 12 months</p>	<p>Self-reported abstinence, verified by expired CO levels &lt;9 ppm or saliva cotinine levels &lt;20 ng/ml            7-day PP abstinence at 2, 6, and 12 months</p>	408 / 294 (72%) / NR

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<b>Bupropion vs. placebo</b>							
Ahluwalia (2002); <sup>158</sup> RCT, double-blind, parallel	To compare a sustained-release form of bupropion hydrochloride with placebo for smoking cessation in African Americans  Bupropion SR was effective for smoking cessation among African American	US (1 site); Government; GlaxoSmithKline provided study medication	7 wks; 26 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Bupropion SR (150 mg) or placebo BID for 7 wks; 8 counselling (45-min) sessions at baseline, wks 1, 3, and 6; telephone at day 3, wks 5 and 7 TQD: 1 wk after start medication	Self-reported abstinence, verified by expired CO levels $\leq 10$ ppm or saliva cotinine levels $\leq 20$ ng/ml 7-day PP abstinence at 6 and 26 wks	600 / 470 (78.3%) / 411 (68.5%)
Aubin (2004); <sup>173</sup> RCT, double-blind, parallel	To confirm the efficacy of bupropion in smoking cessation in European smokers  Bupropion SR is efficacious as an aid to smoking cessation in European smokers	France; multicentre (74 sites); GlaxoSmithKline	7 wks; 26 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Bupropion 150 mg or placebo QD days 1-7, BID from day 7; brief individual counselling at wks 0, 3, 7, 12 and 26; telephone contact at TQD, wks 5 and 18	Self-reported abstinence, verified by expired CO levels $< 10$ ppm 7-day PP abstinence at 7 and 26 wks CAR at wks 4-7, 4-26	504 / NR / 299 (59%)
Brown (2007); <sup>159</sup> RCT, double-blind, parallel	To examine the effects of an intensive cognitive-behavioural mood-	US; multicentre (2 sites); Government	12 wks; 12 months	Bupropion (150 mg, BID) vs. placebo	Treatment: Bupropion 150 mg or placebo QD days 1-3, BID from day 4 All received standard, cognitive behavioural	Self-reported abstinence, verified by expired CO levels $\leq 10$	524 / NR / 426 (81.3%)

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	<p>management treatment of and bupropion, both singularly and in combination, on smoking cessation in adult smokers</p> <p>Bupropion resulted in better smoking outcomes in both intensive group treatments, in comparison with placebo</p>				<p>smoking cessation treatment ± treatment for depression</p> <p>Follow-up: months 2, 6 and 12</p>	<p>ppm and saliva cotinine levels ≤15 ng/ml</p> <p>7-day PP abstinence at end of treatment and follow-ups</p>	
Evins (2001, 2004), <sup>160,181</sup> RCT, double-blind, parallel	<p>To investigate the effect of adding sustained-release bupropion to cognitive behavioural therapy on smoking behaviour and stability of psychiatric symptoms in patients with schizophrenia</p> <p>No evidence of the effect of bupropion was observed in helping patients</p>	US (1site); Government; Glaxo Wellcome Inc. provided bupropion and placebo tablets	12 wks; 2 years	Bupropion (150 mg/day) vs. placebo	<p>Treatment: 12 wks placebo or bupropion 150 mg/day</p> <p>All received 9 weekly group counselling sessions (1 h each) by a nurse and a psychologist</p> <p>Follow-up: wks 4, 8, 12, 14, 18, and 24, and years 1 and 2</p>	<p>Self-reported abstinence, verified by expired-air CO levels &lt;9 ppm or serum cotinine levels &lt;14 ng/ml</p> <p>PP abstinence at 12 and 24 wks , and 2 years</p>	18 / 18 / 17 (94%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	with schizophrenia stop smoking						
Evins (2005); <sup>161</sup> RCT, parallel	To examine the efficacy of bupropion in patients with schizophrenia  Bupropion was modestly effective for smoking cessation in patients with schizophrenia	US (1site); Government; Glaxo Wellcome Inc. provided bupropion and placebo tablets	12 wks; 24 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD days 1-7, BID from day 7 All received a 12-week, 12 sessions group cognitive behavioural therapy by psychologists	Self-reported abstinence, verified by expired-air CO levels <9 ppm 7-day PP abstinence at 12 and 24 wks	53 / 43 (81.1%) / 34 (64%)
Fossati (2007); <sup>174</sup> RCT, double-blind, parallel	To assess the efficacy of bupropion for smoking cessation in primary care  Bupropion doubled the odd of continuous abstinence from smoking	Italy; multicentre (6 sites); Mario Negri Institute; GlaxoSmithKline provided bupropion and placebo tablets	7 wks; 1 year	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for 6 days, BID from 7 wks TQD: 2 <sup>nd</sup> wk after starting medication All received 4 clinical visits and 3 telephone calls	Self-reported abstinence, verified by expired-air CO levels ≤10 ppm CAR at wks 4-7 and wks 4-52 7-day PP abstinence at follow-up visits	593 / NR/ NR
George (2002); <sup>162</sup> RCT, double-blind, parallel	To compare sustained-release bupropion with placebo for smoking cessation	US (1 site); Government; GlaxoSmithKline provided study medication	10 wks; 6 months	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg BID from 10 wks TQD: beginning day 15 of the study	Self-reported abstinence, verified by expired-air CO levels <10	32 / NR / NR

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	<p>in patients with schizophrenic disorders</p> <p>Bupropion enhanced abstinence rates compared with placebo in nicotine-dependent schizophrenic smokers</p>				<p>All received motivational enhanced therapy (wks 1-3); psycho-education, social skills training and relapse prevention strategies (wks 4-10) for a total of 10 wks</p> <p>Follow-up: wks 1, 4, 6, 10, and 6 months</p>	<p>ppm</p> <p>7-day PP abstinence at follow-up visits</p>	
Gonzales (2001); <sup>163</sup> RCT, double-blind, parallel	<p>To assess the safety and efficacy of bupropion as an aid to smoking cessation in smokers treated previously with bupropion</p> <p>Bupropion SR was an effective medication for retreatment of smokers who have used bupropion Sr previously</p>	US; multicentre (16 sites); GlaxoWellcome Inc.	12 wks; 6 months	Bupropion (150 mg, BID) vs. placebo	<p>Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID for remaining 12 wks</p> <p>All received brief individual counselling session at wks 1-7, 9 and 12 of clinical visits and telephone counselling at months 4 and 5</p>	<p>Self-reported abstinence, verified by expired-air CO levels <math>\leq 10</math> ppm</p> <p>CAR at wks 4-7, 9-12 and 4-26</p> <p>7-day PP abstinence at each clinical visit</p>	450 / NR / NR
Haggström (2006); <sup>175</sup> RCT, double-blind, parallel	To compare the efficacy of bupropion and placebo in a group of smokers who	Brazil (1 site); sponsor NR	9 wks; 26 wks	Bupropion (150 mg, BID) vs. placebo	<p>Treatment: Placebo or bupropion 150 mg QD for days 1-5, BID for remaining 9 wks</p> <p>TQD: day 10 after</p>	<p>Self-reported abstinence, verified by expired-air CO levels <math>\leq 10</math></p>	104 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	<p>also received intensive counselling therapy</p> <p>Treatment with bupropion plus CBT resulted in a better 6-month rate of smoking cessation compared to placebo plus CBT</p>				<p>medication</p> <p>All received 6, 15-min individual counselling sessions with cognitive behavioural therapy, weekly during the first month and biweekly during the second month</p> <p>Follow-up: wks 10, 13, and 26</p>	<p>ppm</p> <p>CAR at 3 and 6 months</p>	
Hall (2002); <sup>164</sup> RCT, double-blind, parallel	<p>To examine the efficacy of bupropion with and without psychological intervention</p> <p>Bupropion was efficacious in producing abstinence in cigarette smokers</p>	US (No. of sites NR); Government	12 wks; 52 wks	Bupropion (150 mg, BID) vs. placebo Medical management (MM) vs. psychological intervention (PI)	<p>Four treatment arms:</p> <ol style="list-style-type: none"> <li>1. Bupropion + MM</li> <li>2. Placebo + MM</li> <li>3. Bupropion + PI</li> <li>4. Placebo + PI</li> </ol> <p>Drug: Placebo or bupropion 150 mg QD for days 1-3, BID for remaining 12 wks, then QD for 3 days</p> <p>Medical management (MM): advice to stop smoking, antidepressant medication, adverse effects monitoring, and educational materials</p> <p>Psychological intervention (PI): 5 group sessions; health related</p>	<p>Abstinence verified by CO <math>\leq</math> 10 ppm and urinary cotinine <math>\leq</math> 60 ng/mL, at wks 12, 24, 36, and 52</p> <p>CAR at wks 12, 24, 36, and 52</p>	146 / 124 (85%) / 118 (81%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
					information on mood management and smoking cessation, quit smoking plan, monitoring cigarette use, motivation to quit, relapse prevention, handouts, brief presentations		
Hatsukami (2004); <sup>165</sup> RCT, double-blind, parallel	To determine whether sustained-release bupropion promotes smoking reduction leading to smoking cessation among persons who wish to reduce smoking, but are unwilling or unable to quit  Bupropion SR could increase short-term abstinence rate in smokers initially not willing to quit	US; multicentre (12 sites); GlaxoSmithKline	7 wks; 26 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter All received written materials on smoking reduction techniques; telephone contacts at days 2 and 12 and wk 5 after target reduction date	Self-reported abstinence, verified by expired-air CO levels $\leq 10$ ppm CAR at wks 4-7 and wks 4-26	594 / NR / NR
Hertzberg (2001); <sup>166</sup> RCT, double-blind, parallel	To evaluate the effect of sustained-release bupropion on smoking cessation in patients with chronic	US (1 site); Government; GlaxoWellcome	12 wks; 6 months	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-4, BID thereafter All received individual counselling sessions and self-help booklet on smoking cessation.	Self-reported abstinence, verified by expired-air CO levels $\leq 10$ ppm	15 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	posttraumatic stress disorder No significant difference between groups was observed				Patients were paid \$100 for participation		
Holt (2005); <sup>176</sup> RCT, double-blind, parallel	To determine whether bupropion is effective in the treatment of smoking cessation in the indigenous Maori population in New Zealand  Bupropion was an effective treatment for smoking cessation	New Zealand (1 site); GlaxoSmithKline	7 wks; 12 months	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter TQD: 7-14 days after visit All received motivational telephone call 1 day before and 3 days after TQD Follow-up visits: wks 3 and 7, and months 6, 9, and 12	Self-reported abstinence, verified by expired-air CO (cut-off levels: NR) CAR at all visits	134 / NR/ NR
Hurt (1997); <sup>167</sup> RCT, double-blind, parallel	To compare dose-response of bupropion and placebo for smoking cessation  Bupropion SR was effective for smoking cessation	US; multicentre (3 sites); GlaxoWellcome	7 wks; 52 wks	Bupropion (100 mg, 150 mg, 300 mg/day) vs. placebo	Treatment: 100 mg/d (50 mg BID); 150 mg/d (150 mg each morning, placebo each evening); 300 mg/d (150 mg BID) TQD: after 1 wk of medication All received a brief individual counselling from physician and self-help materials for smoking cessation Follow-up visits: wks 6, 12, 26 and 52	Self-reported abstinence, verified by expired-air CO $\leq 10$ ppm PP abstinence at all follow-up visits	615 / 467 (75.9%) / 396 (64.4%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
McCarthy (2008); <sup>168</sup> RCT, double-blind parallel	To assess the efficacy of bupropion and individual counselling as smoking cessation treatment  Bupropion SR was effective for smoking cessation. Counselling and medication did not interact at any time point	US (No. of sites NR); Government; GlaxoSmithKline provided study medication	9 wks; 52 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-7, BID thereafter TQD: after 1 wk of medication Active ± brief individual counselling vs. placebo ± brief individual counselling Counselling (10 min): 2 pre-quit sessions, 1 session on quit day, and 5 post-quit sessions over the first 4 wks following quit day Follow-up: 8 office visits	Self-reported abstinence, verified by expired-air CO levels ≤10 ppm 7-day PP abstinence at 6 and 12 months	463 / 265 (57.2%) / 292 (63.1%)
Muramoto (2007); <sup>169</sup> RCT, double-blind parallel	To assess the safety and efficacy of sustained-release bupropion for adolescent smoking cessation  Bupropion SR plus brief counselling produced short-term efficacy for adolescent smoking cessation	US; multicentre (2 sites); Government; GlaxoSmithKline	6 wks; 26 wks	Bupropion (150 mg, 300 mg/day) vs. placebo	Treatment: All received placebo or 150 mg QD for days 1-3, followed by 150 mg tablet in the morning and placebo tablet in the evening for 150 mg/d, or 150 mg BID for 300 mg/d, or placebo twice daily All received brief (10-20min) individual counselling at each visit; pre-quit, quit day, then weekly for 7 wks	Self-reported abstinence, verified by expired-air CO levels <10 ppm 7-day PP abstinence at each visit	312 / 262 (84%) / 193 (61.9%)
Rigotti (2006); <sup>170</sup> RCT, double-	To assess the safety and efficacy of 12 wks of	US; multicentre (5 sites); Government; GlaxoSmithKline	12 wks; 1 year	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter	Self-reported abstinence, verified by	248 / NR / 165 (66.5%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
blind parallel	<p>sustained-release bupropion (300 mg) or placebo in smokers admitted for acute cardiovascular disease, primary myocardial infarction, and unstable angina</p> <p>Bupropion SR improved short-term, but not long-term, smoking cessation rates over intensive counselling in hospitalized smokers with acute cardiovascular disease</p>				<p>Treatment began while subjects were in the hospital</p> <p>All received counselling for smoking cessation and relapse prevention, self-help materials and 16-min videotape</p> <p>Counselling began during hospitalization (30-45 min) and continued by telephone (10 min each) 5 times after discharge</p>	<p>saliva cotinine levels <math>\leq 20</math> ng/mL</p> <p>7-day PP abstinence and CAR at 12 and 52 wks</p>	
Simon (2009); <sup>172</sup> RCT, double-blind parallel	<p>To assess the efficacy of sustained-release bupropion for smoking cessation among a population of hospitalized smokers</p> <p>The addition of</p>	US (1 site); Government	7 wks; 6 months	Bupropion (150 mg, BID) vs. placebo	<p>Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter</p> <p>All received cognitive behavioural intervention in an individual counselling session lasted 30-60 min</p> <p>After hospital discharge, all received five follow-up telephone counselling</p>	<p>Self-reported abstinence, verified by salivary cotinine levels <math>&lt; 15</math> ng/mL</p> <p>CAR at 6 months</p>	85 / 74 (87.1%) / 74 (87.1%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	bupropion SR to counselling did not increase quit rates				calls, each lasted 30 min or less. Follow-up at wks 1, 3, 5, 7, and 12 and 6 months		
Tashkin (2001); <sup>171</sup> RCT, double-blind parallel	To assess the efficacy of a 12-wk course of sustained release bupropion in helping patients with stage I and II COPD to stop smoking Bupropion SR was effective aid to smoking cessation in people with mild to moderate COPD	US; multicentre (11 sites); GlaxoWellcome	12 wks; 6 months	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter TQD: 1 wk after starting medication All received telephone counselling 3 days after TQD and brief face-to-face counselling at each clinic visit during the treatment phase (wks 1-7, 10, and 12)	Self-reported abstinence, verified by expired-air CO levels $\leq 10$ ppm CAR at wks 407, 4-12, 4-26 7-day PP abstinence at each clinic visit	411/ 315 (76.6%) / 278 (67.6%)
Tønnesen (2003); <sup>178</sup> RCT, double-blind parallel	To determine whether sustained release bupropion, in combination with counselling, is effective for smoking cessation in a multi-country study Bupropion SR in combination with counselling increased the abstinence rate compared with placebo	Norway, Sweden, Denmark, the Netherlands, France, South Africa, Australia and New Zealand (26 sites); GlaxoSmithKline	7 wks; 12 months	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter TQD: 8-14 days following the baseline visit All received telephone contact at 1 day prior to TQD All received individual counselling at each visit (10-15 min) and telephone contact (5-10 min) to encourage smoking cessation and prevent relapse	Self-reported abstinence, verified by expired-air CO levels $< 10$ ppm CAR and 7-day PP abstinence at each clinic visit	707 / NR / 457 (64.6%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
Tonstad (2003); <sup>179</sup> RCT, double-blind parallel	To investigate the safety and efficacy of sustained release bupropion in promoting abstinence from smoking subjects with cardiovascular disease  Bupropion SR was effective for smoking cessation in smokers with cardiovascular disease	10 countries (28 sites); GlaxoSmithKline	7 wks; 52 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter TQD: 8-14 days following the baseline visit All received telephone contact at 1 day prior to TQD, and motivational support 3 days after All were contacted at monthly intervals to encourage abstinence from smoking and prevent relapse	Self-reported abstinence, verified by expired-air CO levels <10 ppm CAR from wks 4-7, 4-12, 4-26, 4-52 7-day PP abstinence at each clinic visit	626 / NR / 351 (56.1%)
Wagena (2005); <sup>177</sup> RCT, double-blind parallel	To assess the efficacy of sustained release bupropion in smoking cessation among people at risk of or with COPD  Bupropion SR was an efficacious aid to smoking cessation in patients with COPD	The Netherlands (No. of sites NR); Government	12 wks; 26 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-6, BID thereafter TQD: at day 11 from the start of medication All received 3 individual counselling sessions (10-20 min each), and supportive telephone call on the TQD, and wks 2, 4, 6, 8, and 11 after TQD	Self-reported abstinence, verified by urine cotinine values ≤60 ng/mL CAR at wks 4-12, 4-26 7-day PP abstinence at wks 4, 12, 26	175/ 157 (89.7%) / 153 (87.4%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
Zellweger (2005); <sup>180</sup> RCT, double-blind parallel	To evaluate sustained release bupropion for smoking cessation in physicians and nurses  Bupropion Sr was effective for smoking cessation in health care professionals	12 countries (26 sites); GlaxoSmithKline	7 wks; 52 wks	Bupropion (150 mg, BID) vs. placebo	Treatment: Placebo or bupropion 150 mg QD for days 1-3, BID thereafter TQD: within wks 2 of baseline visit All received telephone contact at 1 day prior to TQD, and motivational support 3 days after All were contacted at monthly intervals to encourage abstinence from smoking and prevent relapse	Self-reported abstinence, verified by expired-air CO levels <10 ppm CAR from wks 4-7, 7-12, 52 7-day PP abstinence at each clinic visit	667 / NR / NR
<b>Bupropion vs. nicotine patch</b>							
Uyar (2007); <sup>182</sup> RCT, parallel	To assess the effectiveness and side effect profiles of nicotine patch and bupropion therapies for smoking cessation  No differences were observed between groups	Turkey (1 site); sponsor NR	6 wks; 24 wks	Nicotine patch vs. bupropion (150 mg, BID)	Two treatment arms: 1. Nicotine patch: 21 mg for 2 wks, 14 mg for 2 wks, and 7 mg for 2 wks 2. Bupropion: 150 mg QD for days 1-3, BID thereafter to 6 wks  Follow-up visits: wks 2, 4, 6, 8, 12, and 24	Self-reported abstinence, verified by expired-air CO levels <10 ppm PP abstinence at each clinic visit	100 / NR / NR
<b>Bupropion vs. bupropion + counselling</b>							
McCarthy (2008); <sup>168</sup> RCT, double-	To assess the efficacy of bupropion and	US (No. of sites NR); Government; GlaxoSmithKline provided	9 wks; 52 wks	Bupropion (150 mg, BID) vs. bupropion +	Treatment: Bupropion 150 mg QD for days 1-7, BID thereafter	Self-reported abstinence, verified by	229 / 133 (58.1%) / 148 (64.6%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
blind parallel	individual counselling as smoking cessation treatment  Counselling and medication did not significantly interact at any time point	study medication		counselling	TQD: after 1 wk of medication Counselling (10 min): 2 pre-quit sessions, 1 session on quit day, and five post-quit sessions over the first 4 wks following quit day No counselling: psychoeducation session on medication use, adherence, info on target quit day, general support and encouragement Follow-up: 8 office visits	expired-air CO levels $\leq 10$ ppm 7-day PP abstinence at 6 and 12 months	
<b>Nicotine patch + nicotine nasal spray vs. nicotine patch + placebo spray</b>							
Blondal (1999); <sup>183</sup> RCT, double-blind parallel	To evaluate the efficacy of using a nicotine patch for 5 months with a nicotine nasal spray for 1 year The combination of using nicotine patch for 5 months with a nicotine nasal spray for 1 year was a more effective method of stopping smoking than using a patch only	Iceland (1 site); Pharmacia and Upjohn	5 months on patch and 1 year on spray; up to 6 years	Patch + spray vs. patch + placebo spray	Details on treatment with nicotine patch and nicotine nasal spray (0.5 mg/dose): NR  Supportive group meetings held at 1, 8, 15, and 22 days after stopping smoking Individual follow-up: days 15 and 43, months 3 and 6, and years 1 and 6	Self-reported abstinence, verified by expired-air CO levels $< 10$ ppm CAR at each follow-up	239 / 237 (99.2%) / 235 (98.3%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
<b>Nicotine inhaler + nicotine patch vs. nicotine inhaler + placebo patch</b>							
Bohadana (2000, 2003); <sup>184,364</sup> RCT, double-blind parallel	To compare the efficacy of nicotine inhaler plus nicotine patch vs. nicotine inhaler plus placebo patch for smoking cessation Treatment with the nicotine inhaler plus nicotine patch resulted in significantly higher cessation rates than inhaler plus placebo patch	France (1 site); Pharmacia and Upjohn	26 wks (6 wks double-blind, 6 wks single blind, then open thereafter); 12 months	Inhaler + patch vs. inhaler + placebo patch	Nicotine inhaler: plastic tube with 10 mg nicotine; puff shallowly about 10 times more often than when smoking a cigarette Nicotine patch: 30 cm <sup>2</sup> patch delivered 15 mg nicotine per 16 h. Placebo patch was the same size and appearance Follow-up visits: wks 1, 2, 6, and 12, and months 6 and 12	Self-reported abstinence, verified by expired-air CO levels <10 ppm CAR at each follow-up	400 / 133 (33.3%) / 97 (24.3%)
<b>Bupropion + nicotine gum vs. bupropion + placebo gum vs. placebo bupropion + placebo gum</b>							
Piper (2007); <sup>187</sup> RCT, double-blind parallel	To determine the efficacy of the combination of bupropion and nicotine gum, bupropion alone, and a placebo condition in promoting smoking cessation Adding nicotine gum to bupropion did not increase abstinence rate	US (No. of sites NR); Government	9 wks; 12 months	Bupropion + gum vs. bupropion + placebo gum vs. two placebos	Bupropion (150 mg, BID); 4 mg nicotine gum (12 pieces of gum/d) for 9 wks TQD: 1 wk after beginning medication All received 3 brief (10-min) counselling sessions over 3 wks	Self-reported abstinence, verified by expired-air CO or serum cotinine (cut-off levels: NR) 7-day PP abstinence at 6 and 12 months	608 / 526 (86.5%); 417 (68.6%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
<b>NRT + bupropion vs. NRT + placebo bupropion</b>							
Evins (2007); <sup>191</sup> RCT, double-blind parallel	To examine whether there is a benefit of adding sustained release bupropion to high-dose combination NRT and weekly group cognitive-behavioural therapy for smoking reduction or cessation in schizophrenia  Abstinence rates did not differ between treatment groups	US; multicentre (4 sites); Government; GlaxoSmithKline provided bupropion and placebo	12 wks; 12 months	NRT + bupropion vs. NRT + placebo	Bupropion or placebo: 150 mg QD for 7 days, then BID for 11 wks Nicotine patch: 21 mg/d for 4 wks, 14 mg/d for 2 wks, and 7 mg/d for 2 wks Nicotine gum (2 mg) was distributed for use as needed for craving, up to 18 mg/d All received psychological treatments	Self-reported abstinence, verified by expired-air CO levels <8 ppm CAR at 12 months	51 / 38 (74.5%) / NR
George (2008); <sup>190</sup> RCT, double-blind parallel	To determine whether the combination of sustained release bupropion + nicotine patch was well-tolerated and superior to placebo + patch for smoking cessation in schizophrenia  Combination therapy with	US (1 site); Government	10 wks; 6 months	Nicotine patch + bupropion vs. nicotine patch + placebo	Bupropion or placebo: started on day 8, 150 mg QD for 3 days, then BID for 10 wks Nicotine patch: 21 mg/d applied at day 15 and continued until day 70 All received 10 weekly sessions of group behavioural therapy (50 min)	Self-reported abstinence, verified by expired-air CO levels <10 ppm 7-day PP abstinence at 6 months	58 / NR / 42 (72.4%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	bupropion and nicotine patch versus placebo and nicotine patch significantly improved short-term smoking abstinence in smokers with schizophrenia						
Killen (2004); <sup>192</sup> RCT, double-blind parallel	To determine the efficacy of nicotine patch + bupropion compared with nicotine patch + placebo in treatment of adolescent smokers  Abstinence rates did not differ between treatment groups	US; high schools (9 sites); Government; GlaxoSmithKline provided study medication	9 wks; 26 wks	Nicotine patch + bupropion vs. nicotine patch + placebo	Bupropion or placebo: 150 mg/day for 9 wks Nicotine patch: 8 wks; if smoked >15 cigarettes/day: 21-mg for 4 wks, 14-mg for 2 wks and 7-mg for 2 wks; if smoked between 10-15 cigarettes/day: 14-mg for 6 wks and 7-mg for 2 wks All received weekly group skill training (45-min session)	Self-reported abstinence, verified by expired-air CO levels <9 ppm or saliva cotinine level <20 ng/mL 7-day PP abstinence at end of treatment and 26 wks	211 / NR / NR
Simon (2004); <sup>193</sup> RCT, double-blind parallel	To determine the efficacy of nicotine patch + bupropion compared with nicotine patch + placebo for smoking cessation  Abstinence rates did not differ	US (1 site); Government	8 wks; 1 year	Nicotine patch + bupropion vs. nicotine patch + placebo	7-wk course of bupropion or placebo: 150 mg QD for 3 days, then BID thereafter Nicotine patch: 21 mg/d for 4 wks, 14 mg/d for 2 wks, and 7 mg/d for 2 wks All received individual counselling sessions (30-	Self-reported abstinence, verified by saliva cotinine levels <15 ng/mL 7-day PP abstinence at 6 and 12 months CAR at 12	244 / NR / 236 (96.7%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	between treatment groups				60 min) and 5 follow-up counselling calls	months	
<b>Bupropion + nicotine patch vs. bupropion + placebo vs. nicotine patch + placebo vs. placebo</b>							
Jorenby (1999); <sup>188</sup> Smith (2003); <sup>197</sup> RCT, double-blind parallel	To assess the efficacy of bupropion, placebo, nicotine patch and combination of bupropion and nicotine patch in smoking cessation Treatment with bupropion SR alone or in combination with nicotine patch resulted in significantly higher long term rates of smoking cessation than use either nicotine patch alone or placebo	US; multicentre (4 sites); Glaxo Wellcome	9 wks; 12 months	Bupropion + nicotine patch vs. bupropion + placebo patch vs. nicotine patch + placebo bupropion vs. two placebos	7-wk course of placebo or bupropion 150 mg QD for 3 days, then BID thereafter Nicotine patch: 21 mg/d for 4 wks, 14 mg/d for 2 wks, and 7 mg/d for 2 wks TQD: day 8 All received brief (~15 min) individual counselling session for smoking cessation at each clinic visits and follow-up counselling (~10 min)	Self-reported abstinence, verified by expired-air CO levels ≤10 ppm 7-day PP abstinence at 6 and 12 months	893 / 582 (65.2%) / NR
<b>Nicotine patch + nicotine gum vs. nicotine patch + placebo gum vs. placebo</b>							
Kornitzer (1995); <sup>185</sup> RCT, double-blind parallel	To evaluate the possible beneficial effects of adding nicotine gum to the routine of subjects using nicotine patch	Belgium and Sweden (3 sites); Pharmacia	24 wks; 12 months	Patch + gum vs. patch + placebo gum vs. two placebos	Nicotine patch: 12 wks with 15-mg patch /16 h, 6 wks with 10-mg, 6 wks with 5-mg Nicotine gum: 2-mg, not restricted during the first 6 months, to use at least 4	Self-reported abstinence, verified by expired-air CO levels <10 ppm CAR at each	374 / NR / NR

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/completed treatment/completed study
	Adding nicotine gum to nicotine patch increased abstinence rates				pieces/day	visit	
Cooney (2009); <sup>186</sup> RCT, double-blind parallel	To compare the efficacy of smoking cessation treatment using a combination of nicotine patch plus nicotine gum versus nicotine patch plus placebo gum in alcohol-dependent subjects Nicotine patch plus gum was more effective than nicotine patch alone for smoking cessation	US (2 sites); Government	12 weeks patch, 24 weeks gum; 1 year	Patch + gum vs. patch + placebo gum	Nicotine patch: 8 wks with 21-mg patch /d, 2 wks with 14-mg patch /d, 2 wks with 7-mg patch /d Nicotine gum: 2-mg, 6-20 pieces/d, up to 24 wks Behaviour therapy for alcohol dependence and smoking: 3 months of weekly sessions (60 min of individual treatment) followed by 3 monthly booster sessions	Self-reported abstinence, verified by expired-air CO levels <10 ppm PAR at each follow-up visit (2 wks and 3, 6 and 12 months)	96 / 79 (82.3%) / 69 (71.9%)
<b>Nicotine patch + nicotine inhaler + bupropion vs. nicotine patch</b>							
Steinberg (2009); <sup>189</sup> RCT, parallel	To evaluate extended duration of a triple-medication combination versus standard duration therapy with nicotine patch alone The combination	US (1 site); Government and public funding	10 wks on patch, variable on combination; 26 wks	Patch + inhaler + bupropion vs. patch	Nicotine patch (10 wks): 21 mg/d for 6 wks, 14 mg/d for 2 wks and 7 mg/d for 2 wks Nicotine inhaler (to be used as needed) Bupropion: 150 mg/day The duration of treatment of the combination group was symptom-triggered	Self-reported abstinence, verified by expired-air CO levels ≤8 ppm 7-day PP abstinence at 26 wks	127 / 119 (93.7%) / 96 (75.6%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	group had higher abstinence rates than nicotine patch group				Follow-up: wks 2, 4, 8, 12, 16, 20, 24, and 26		
<b>No pay vs. pay</b>							
Hays (1999); <sup>62</sup> RCT, parallel	To determine the efficacy and safety of the nicotine patch for smoking cessation in an over-the-counter environment Abstinence rates did not differ between pay and no-pay of over-the-counter nicotine patch	US; multicentre (3 sites); Elan Pharmaceutical Research Corp.	6 wks; 24 wks	No pay vs. pay	Advertisement for volunteers Treatment: 6 wks, 22 mg QD Follow-up: 12 and 24 wks All received instructions for patch use and self-help pamphlet, with no counselling or advice Subjects in open label-pay trial were required to purchase nicotine patches (\$21/wk)	Self reported abstinence, verified by CO levels $\leq 8$ ppm 7-day PP abstinence at 6 months	643 / NR/ NR
Kaper (2005); <sup>195</sup> RCT, parallel	To examine the effects of financial reimbursement for all smoking cessation treatments that have been shown to be efficacious and are available in the Netherlands Reimbursement seems efficacious in increasing the use of smoking	The Netherlands (No. of sites NR); Stivoro	6 months; 6 months	Reimbursement vs. no reimbursement	Pharmacological treatment: bupropion and NRT (gum, patch, sublingual, inhaler); behavioural counselling (written advice, telephone, face-to-face); or combination For a period of 6 months, smokers in the intervention group had the opportunity to apply for full reimbursement. They received	Self reported abstinence, verified by CO levels $< 7$ ppm 7-day PP abstinence at 6 months	1266 / 947 (74.8%) / 947 (74.8%)

First author, Year; Design	Objective / Conclusion	Countries; Setting (No. of centres); Sponsor	Treatment duration; Length of follow-up	Comparison arms	Description of intervention and comparator	Efficacy evaluations	No. of patients assigned/ completed treatment/ completed study
	cessation treatment and may double the number of successful quitters				information on how to receive the reimbursement		
Volpp (2009); <sup>194</sup> RCT, parallel	To assess the financial incentives for smoking cessation among employees of a multinational company based in the US  Financial incentives for smoking cessation significantly increased the rates of smoking cessation	US; multicentre (No. of sites NR); Government	NR; 18 months	Incentive vs. control	Financial incentives: \$100 for completion of a smoking cessation program, \$250 for cessation smoking within 6 months after study enrollment, and \$400 for abstinence for an additional 6 months after the initial cessation; as confirmed by biochemical test All received information about community-based smoking cessation resources within 20 miles of their work site, and standard health benefits provided by the firm (physician visits' coverage, bupropion and other prescribed smoking cessation drugs) Follow-up: months 3, 6, 9, 12, 15 and 18	Self reported abstinence, verified by saliva cotinine levels <15 ng/ml or urine cotinine levels <2 ng/ml 7-day PP abstinence at each follow-up CAR at 6 and 12 months	878 / 753 (85.8%) / 643 (73.2%)

BID: twice daily ;CAR: continuous abstinence rate; CO: carbon monoxide; min: minute; NA: not applicable; NRT: nicotine replacement therapy; pp: point prevalence; ppm: part per million; PAR: prolonged abstinence rate; QD: once a day; TQD: target quit date; Wks: weeks;

## Appendix 6b: Patient baseline characteristics

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
<b>Varenicline vs. placebo</b>								
Nakamura (2007); <sup>47</sup> RCT, parallel	<i>Inclusion:</i> Japanese smokers (age 20-75 years); healthy and motivated-to-quit; smoked at least 10 cigarettes per day; no period of abstinence >90 days  <i>Exclusion:</i> Serious diseases (cardiovascular, cerebrovascular, and pulmonary disease; cancer; hepatic or renal impairment; neurologic or psychiatric disorder); laboratory abnormalities; BMI <15 or >38 kg/m <sup>2</sup> ; body weight <45 kg; history of substance abuse; use of other tobacco products; refusal to abstain	Varenicline (0.25 mg BID)	128 (93/35)	40.2 ± 12.3	20.9 ± 11.5	24.9 ± 10.3	5.6 ± 2.1	NR
		(0.5 mg BID)	128 (91/37)	39.0 ± 12.0	20.1 ± 11.3	23.8 ± 10.5	5.5 ± 2.1	NR
		(1 mg BID)	130 (103/27)	40.1 ± 11.6	21.5 ± 11.3	24.0 ± 9.8	5.4 ± 2.1	NR
		Placebo	129 (98/31)	39.9 ± 12.3	20.9 ± 11.4	23.1 ± 8.8	5.7 ± 1.8	NR
Niaura (2008); <sup>48</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit healthy adult smokers (age 18-65 years); smoked at least 10 cigarettes per day; no period of abstinence >3 months  <i>Exclusion:</i> Significant allergies; serious diseases (endocrine, gastrointestinal, hematological, hepatic, neurological, psychiatric, pulmonary, renal or cardiovascular); cancer; hypertension; psychiatric disorder; substance abuse (within 12 months of study)	Varenicline (0.5-2.0 mg daily)	157 (79/78)	41.5 ± 11.3	24.9 (range: 4-50)	22.2 (range: 10-60)	5.40	NR
		Placebo	155 (83/72)	42.1 ± 11.7	25.7 (range: 2-46)	22.3 (range: 6-60)	5.35	NR
Oncken (2006); <sup>49</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Healthy smokers (age 18-65 years); smoked ≥10 cigarettes per day  <i>Exclusion:</i> Treatment with an investigational drug within the previous month; major depression; psychiatric	Varenicline (0.5 mg BID non-titrated)	129 (58/71)	42.9 ± 10.1	26.0 ± 10.8	20.9 ± 8.1	5.5 ± 2.0	NR
		Varenicline (0.5 mg BID titrated)	130 (69/61)	43.5 ± 10.5	25.0 ± 10.8	21.3 ± 8.1	5.4 ± 1.9	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	disorders; use of NRT or bupropion within the previous 3 months; cardiovascular disease; significant medical disease; substance abuse; use of other forms of tobacco	Varenicline (1.0 mg BID non-titrated)	129 (63/66)	43.7 $\pm$ 10.0	25.7 $\pm$ 10.6	20.8 $\pm$ 10.1	5.5 $\pm$ 2.0	NR
		Varenicline (1.0 mg BID titrated)	130 (63/67)	42.2 $\pm$ 10.7	24.0 $\pm$ 11.1	20.9 $\pm$ 7.0	5.3 $\pm$ 2.1	NR
		Placebo	129 (67/62)	43.0 $\pm$ 9.4	25.3 $\pm$ 9.5	20.4 $\pm$ 7.2	5.8 $\pm$ 2.3	NR
Tsai (2007); <sup>50</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit healthy adult smokers (age 18-75 years); smoked $\geq$ 10 cigarettes per day; no period of abstinence >3 months  <i>Exclusion:</i> Pregnant or breastfeeding women; serious diseases (cardiovascular, cerebrovascular, endocrine, gastrointestinal, pulmonary); hepatic or renal impairment; neurologic or psychiatric disorders; BMI <15 or >38 kg/m <sup>2</sup> ; body weight <45 kg; history of substance abuse	Varenicline (1.0 mg BID)	126 (107/19)	39.7 $\pm$ 9.3 (range: 21-62)	20.2 (range: 3-45)	23.4 (range: 10-60)	5.2 $\pm$ 2.4	NR
		Placebo	124 (115/9)	40.9 $\pm$ 11.1 (range: 23-73)	22.1 (range: 3-52)	22.7 (range: 10-60)	5.0 $\pm$ 2.3	NR
Wang (2009); <sup>51</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit healthy adult smokers (age 18-75 years); smoked $\geq$ 10 cigarettes per day; no period of abstinence >3 months; BMI 15-38 kg/m <sup>2</sup> ; weight $\geq$ 45.5 kg  <i>Exclusion:</i> Depression; psychological disorders; serious diseases (endocrine, gastrointestinal, COPD, cardiovascular, neurologic, cerebrovascular); hypertension; hepatic or renal impairment; cancer; allergy to drugs; substance abuse; pregnancy	Varenicline (1.0 mg BID)	165 (159/6)	39.0	20.5	20.3	5.27	NR
		Placebo	168 (163/5)	38.5	19.6	21.3	5.51	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
Williams (2007); <sup>52</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit healthy adult smokers (age 18-75 years); smoked ≥10 cigarettes per day; no period of abstinence >3 months  <i>Exclusion:</i> Pregnancy or lactation; history of cancer; cardiovascular diseases; hypertension; use of other forms of tobacco products; use of psychoactive drugs or NRT during the study	Varenicline (1.0 mg BID)	251 (127/124)	48.2 ± 12.3 (range: 18-75)	30.7 (range: 4-57)	23.2 (range: 10-90)	5.5 ± 2.07	NR
		Placebo	126 (61/65)	46.6 ± 12.1 (range: 18-74)	29.9 (range: 6-57)	23.4 (range: 10-50)	6.05 ± 1.94	NR
<b>Varenicline vs. bupropion vs. placebo</b>								
Gonzales (2006); <sup>54</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit healthy adult smokers (age 18-75 years); smoked ≥10 cigarettes per day; no period of abstinence >3 months  <i>Exclusion:</i> Serious or unstable disease within previous 6 months; seizure; diabetes; hepatic or renal impairment; COPD; cancer; significant allergic reactions; depression; mental disorders; substance abuse; BMI <15 or >38 kg/m <sup>2</sup> ; body weight <45 kg; prior exposure to bupropion or varenicline; pregnancy	Varenicline (1.0 mg BID)	352 (176/176)	42.5 ± 11.1	24.3 ± 11.5	21.1 ± 9.47	5.18 ± 2.16	NR
		Bupropion (150 mg BID)	329 (192/137)	42.0 ± 11.7	24.1 ± 11.5	21.0 ± 8.52	5.19 ± 2.08	NR
		Placebo	344 (186/158)	42.6 ± 11.8	24.7 ± 12.1	21.5 ± 9.51	5.38 ± 1.99	NR
Jorenby (2006); <sup>55</sup> RCT, parallel (phase 3 trial)	<i>Inclusion:</i> Motivated-to-quit healthy adult smokers (age 18-75 years); smoked ≥10 cigarettes per day; no period of abstinence >3 months  <i>Exclusion:</i> Serious or unstable disease	Varenicline (1.0 mg BID)	344 (190/154)	44.6 ± 11.4	27.1 ± 11.5	22.5 ± 9.5	5.39 ± 2.21	NR
		Bupropion (150 mg BID)	342 (206/136)	42.9 ± 11.9	25.4 ± 12.0	21.8 ± 8.7	5.39 ± 2.19	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
	within previous 6 months; seizure; diabetes; hepatic or renal impairment; COPD; cancer; significant allergic reaction; depression; mental disorders; substance abuse; BMI <15 or >38 kg/m <sup>2</sup> ; body weight <45 kg; prior exposure to bupropion or varenicline; pregnancy	Placebo	341 (198/143)	42.3 ± 11.6	24.4 ± 11.6	21.5 ± 8.7	5.16 ± 2.19	NR
Nides (2006); <sup>56</sup> RCT, parallel (phase 2 trial)	<i>Inclusion:</i> Healthy adult smokers (age 18-65 years); smoked ≥10 cigarettes per day; no period of abstinence >3 months  <i>Exclusion:</i> Major depression; psychotic disorders; seizures; cardiovascular disease; hypertension; allergy; renal, endocrine, pulmonary, hepatic, gastrointestinal or neurologic diseases; substance abuse	Varenicline (0.3 mg QD)	126 (63/63)	41.9 ± 10.6	24.6 ± 10.9	20.3 ± 7.7	5.7 ± 2.1	NR
		(1.0 mg QD)	126 (55/71)	42.9 ± 10.5	25.4 ± 11.1	20.1 ± 7.8	5.5 ± 2.0	NR
		(1.0 mg BID)	125 (63/62)	41.9 ± 9.8	23.4 ± 10.0	18.9 ± 6.9	5.6 ± 2.0	NR
		Bupropion (150 mg BID)	126 (57/69)	40.5 ± 10.8	23.4 ± 10.9	19.5 ± 6.9	5.2 ± 1.9	NR
		Placebo	123 (64/59)	41.6 ± 10.4	23.9 ± 10.6	21.5 ± 8.0	5.5 ± 2.3	NR
<b>Varenicline vs. nicotine patch</b>								
Aubin (2008); <sup>57</sup> RCT, parallel (phase 3 trial)	<i>Inclusion:</i> Healthy adult smokers (age 18-75 years); smoked ≥15 cigarettes per day; no period of abstinence >3 months; weight >45.5 kg; BMI 15-38 kg/m <sup>2</sup>  <i>Exclusion:</i> Pregnancy, breastfeeding or risk becoming pregnant; cancer, serious diseases; psychological disorders; allergy; skin disorders; hypertension; renal or hepatic impairment; previous use of NRT in previous 6 months or varenicline in previous year	Varenicline (1.0 mg BID)	376 (182/194)	42.9 ± 10.5	25.9 (range: 2-58)	23.0 (range: 15-80)	5.62 ± 2.23	NR
		Nicotine patch	370 (185/185)	42.9 ± 12.0	25.2 (range: 1-62)	22.4 (range: 11-60)	5.37 ± 1.99	NR
<b>Nicotine patch vs. placebo</b>								
Campbell (1996); <sup>71</sup> RCT, parallel	<i>Inclusion:</i> Hospital inpatients and outpatients with smoking-related respiratory disease or CVD (age 18-75 years); willing to try to stop smoking;	Nicotine patch	115 (53/62)	49.0 ± 13.3	31 ± 13	NR	NR	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
	smoked >1 cigarettes daily in the previous wk  <i>Exclusion:</i> Cigar or pipe smokers; allergic to cutaneous application; skin disease; myocardial infarction; cardiac arrhythmias; pregnancy or lactation; cancer; mental disturbances	Placebo	119 (55/64)	49.0 ± 13.3	31 ± 13	NR	NR	NR
Davidson (1998); <sup>58</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age >18 years), regardless of medical illness or concomitant medication; smoking ≥1 year; ≥20 cigarettes per day  <i>Exclusion:</i> Pregnancy; myocardial infarction	Nicotine patch	401 (189/212)	39.29 ± 12.28	21.52 ± 11.85	29.79 ± 10.65	NR	NR
		Placebo	401 (184/217)	39.60 ± 11.46	21.41 ± 11.12	29.14 ± 9.98	NR	NR
Daughton (1991); <sup>59</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Recruited smokers (age 21-64 years), normal health; smoking ≥1 year, ≥1 pack per day  <i>Exclusion:</i> NR	Nicotine patch (24 h)	51 (NR/NR)	41.8 (range 21-64)	23.9 (range 3-48)	32.9 (20-99)	7.0 (range 3-11)	NR
		Nicotine patch (16 h)	55 (NR/NR)					NR
		Placebo	52 (NR/NR)					NR
Daughton (1998); <sup>60</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers (age 19-65 years) referred by family physicians; smoking ≥1 year, ≥20 cigarettes per day  <i>Exclusion:</i> Skin disease; current use of psychotropic drugs; substance abuse; angina pectoris; cardiac arrhythmias; myocardial infarction; pregnancy or lactation	Nicotine patch	184 (71/113)	37.9 ± 9.7	19.3 ± 9.2	27.2 ± 8.2	6.9 ± 1.8	NR
		Placebo	185 (77/108)	36.7 ± 8.8	19.8 ± 9.1	29.8 ± 9.1	7.2 ± 1.7	NR
Fiore (1994); <sup>61</sup> RCT, double-	<u>Study 1:</u> <i>Inclusion:</i> Motivated-to-quit smokers (age 21-65 years); CO levels ≥10 ppm; smoking	Nicotine patch	44 (19/25)	43.3 ± 9.9	25.2 ± 8.6	28.3 ± 7.3	7.3 ± 1.3	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
blind, parallel	$\geq 15$ cigarettes/day for $\geq 1$ year <i>Exclusion:</i> Cardiovascular disease; pregnancy or lactation; use of psychotropic drug; substance abuse; psychiatric disorders; dermatologic disorders	Placebo	43 (19/24)	42.6 $\pm$ 9.2	24.3 $\pm$ 9.2	30.3 $\pm$ 9.8	6.9 $\pm$ 1.3	NR
	<u>Study 2:</u> <i>Inclusion:</i> Motivated-to-quit smokers (age 21-65 years); CO levels $\geq 10$ ppm; smoking $\geq 15$ cigarettes/day for $\geq 1$ year <i>Exclusion:</i> Cardiovascular disease; pregnancy or lactation; use of psychotropic drug; substance abuse; psychiatric disorders; dermatologic disorders	Nicotine patch	57 (18/39)	43.1 $\pm$ 9.1	24.3 $\pm$ 9.1	29.8 $\pm$ 9.8	7.2 $\pm$ 1.5	NR
		Placebo	55 (18/37)	44.2 $\pm$ 11.1	25.9 $\pm$ 10.4	30.8 $\pm$ 9.6	7.7 $\pm$ 1.5	NR
Glavas (2003); <sup>75</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Recruited health professionals at a university hospital (age $>18$ years); willing-to-quit; smoking for $\geq 12$ months <i>Exclusion:</i> Pregnancy or lactation; other drug dependence; major psychiatric disorders; skin disease	Nicotine patch	56 (19/37)	34.4 $\pm$ 4.7	16.4 $\pm$ 4.7	24.1 $\pm$ 5.8	6.8 $\pm$ 1.5	2.3 $\pm$ 2.2
		Placebo	56 (19/37)	33.8 $\pm$ 4.4	16.5 $\pm$ 4.1	22.5 $\pm$ 5.7	6.9 $\pm$ 1.1	2.3 $\pm$ 1.6
Hays (1999); <sup>62</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $>18$ years); smoked $\geq 1$ year; smoked $\geq 15$ cigarettes per day during the previous 6 months <i>Exclusion:</i> Pregnancy or lactation; use of any tobacco products other than cigarettes; use of other forms of nicotine; recent MIT (1 month)	Nicotine patch	321 (156/165)	43.5 $\pm$ 11.2	25.2 $\pm$ 11.4	Range: 16 to $>40$	6.1 $\pm$ 2.0	NR
		Placebo	322 (169/153)	44.1 $\pm$ 11.6	25.9 $\pm$ 11.9	Range: 16 to $>40$	6.3 $\pm$ 2.0	NR
Hughes (2003); <sup>63</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $>18$ years); smoked at least 20 cigarettes per day; past alcohol dependence	Nicotine patch	61 (44/17)	43 $\pm$ 8	NR	30 $\pm$ 11	7.9 $\pm$ 1.8	9.4 $\pm$ 20.1

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	<i>Exclusion:</i> Substance abuse for $\leq 30$ days; cardiac or dermatology disorders; psychiatric disorder; woman using birth control; using disulfiram or naltrexane	Placebo	54 (34/20)	43 $\pm$ 9	NR	29 $\pm$ 11	7.6 $\pm$ 1.6	3.7 $\pm$ 4.6
Hurt (1994), <sup>64</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit and healthy smokers (age 20-65 years); smoked $\geq 20$ cigarettes per day; CO levels $\geq 10$ ppm  <i>Exclusion:</i> Recent (6 months) heart and cardiovascular disease; substance abuse; psychiatric disorder; pregnancy or lactation; skin disease; use of other form of nicotine or drugs that might interfere the study	Nicotine patch	120 (58/62)	42.8 $\pm$ 11.1 (range: 20-65)	23.7 $\pm$ 10.4	28.8 $\pm$ 9.4	6.3 $\pm$ 2	NR
		Placebo	120 (53/67)	43.6 $\pm$ 10.6 (range: 21-65)	25.8 $\pm$ 10.7	30.6 $\pm$ 9.4	6.8 $\pm$ 2	NR
ICR group (1993, 1994, 2003), <sup>72,355,356</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit and healthy smokers (age 25-64 years); smoked $\geq 15$ cigarettes per day  <i>Exclusion:</i> Skin hypersensitivity to nicotine; skin disease; cancer; cerebrovascular or cardiovascular diseases; pregnancy or lactation; use of other forms of nicotine	Nicotine patch	842 (393/449)	42.4 $\pm$ 9.8	25.0 $\pm$ 10	24.5 $\pm$ 8.3	NR	2 (range 0-50)
		Placebo	844 (364/480)	42.9 $\pm$ 10	25.3 $\pm$ 10	24.2 $\pm$ 8.1	NR	2 (range 0-50)
Killen (1997), <sup>65</sup> RCT, parallel	<i>Inclusion:</i> Recruited smokers (age $\geq 18$ years)  <i>Exclusion:</i> Pregnancy or lactation; cancer; peptic ulcer; those with heart disease, chest pain, diabetes or thyroid disease needed permission from physicians	Nicotine patch	212 (109/103)	46.2 $\pm$ 11	NR	24.0 $\pm$ 9.3	Modified	NR
		Placebo	212 (105/107)	44.6 $\pm$ 11.4	NR	23.1 $\pm$ 8.7	Modified	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Lewis (1998); <sup>66</sup> RCT, parallel	<p><i>Inclusion:</i> Motivated-to-quit hospitalized inpatient smokers (age <math>\geq 18</math> years); smoked <math>\geq 10</math> cigarettes/day; medical appropriateness for nicotine patch treatment</p> <p><i>Exclusion:</i> Substance abuse; psychiatric illness; pregnancy or lactation; use of other forms of nicotine products; skin disorders; discharged within 24 h of admission; admission to intensive care unit; heart disease</p>	Nicotine patch	62 (35/27)	43.4 $\pm$ 13.6	26.3 $\pm$ 13.4	24.0 $\pm$ 15.8	NR	NR
		Placebo	62 (30/32)	44.7 $\pm$ 13.6	27.5 $\pm$ 13.8	24.9 $\pm$ 10.9	NR	NR
Oncken (2007); <sup>67</sup> RCT, double-blind, parallel	<p><i>Inclusion:</i> Motivated-to-quit postmenopausal smokers; smoked <math>\geq 10</math> cigarettes per day</p> <p><i>Exclusion:</i> Alcoholism; use of other forms of nicotine; psychiatric disorders; unstable angina; myocardial infarction; received treatment with bupropion; use of medications that affect bone metabolism; receiving treatment for osteoporosis</p>	Nicotine patch	57 (0/57)	54.0 $\pm$ 6.9	33.4 $\pm$ 10.4	21.6 $\pm$ 8.0	6.0 $\pm$ 2.0	NR
		Placebo	95 (0/95)	56.6 $\pm$ 6.9	35.1 $\pm$ 9.9	21.4 $\pm$ 8.4	5.5 $\pm$ 1.8	NR
Paoletti (1996); <sup>76</sup> RCT, double-blind, parallel	<p><i>Inclusion:</i> Motivated-to-quit smokers (age <math>\geq 20</math> years); smoked <math>\geq 10</math> cigarettes per day, for <math>\geq 3</math> years</p> <p><i>Exclusion:</i> Skin disorders; cardiac diseases; use of psychotropic drugs; pregnancy or lactation</p>	Nicotine patch 15 mg (cotinine $\leq 250$ ng/ml)	60 (35/25)	41 $\pm$ 10	NR	24 $\pm$ 10	5.2 $\pm$ 2.1	NR
		Placebo (cotinine $\leq 250$ ng/ml)	60 (28/32)	44 $\pm$ 10	NR	23 $\pm$ 7	5.4 $\pm$ 2.4	NR
		Nicotine patch 15 mg (cotinine $> 250$ ng/ml)	90 (62/28)	42 $\pm$ 9	NR	30 $\pm$ 11	7.0 $\pm$ 1.9	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
		Nicotine patch 25 mg (cotinine >250 ng/ml)	87 (54/33)	42 $\pm$ 9	NR	30 $\pm$ 9	7.0 $\pm$ 1.8	NR
Richmond (1994, 1997, 2007); <sup>77,357-359</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Recruited smokers (age 17-70 years); smoked $\geq$ 20 cigarettes per day <i>Exclusion:</i> Pregnancy or lactation; heart disease; skin disease; psychological disorders; use of other forms of nicotine; do not speak English; peptic ulcer	Nicotine patch	156 (75/81)	42 $\pm$ 11.5	24.3 $\pm$ 11.1	28.5 $\pm$ 11.4	6.0 $\pm$ 2.2	NR
		Placebo	157 (75/82)	41 $\pm$ 10.5	23.6 $\pm$ 10.4	303 $\pm$ 14.3	6.3 $\pm$ 2.3	NR
Russell (1993); <sup>73</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 20-60 years); smoked $\geq$ 15 cigarettes per day <i>Exclusion:</i> Cardiovascular disease; hypertension; diabetes; on psychotropic medication; pregnancy or lactation; skin diseases; allergy; use of nicotine gum in the past 3 months	Nicotine patch	400 (142 / 258)	39.3 $\pm$ 9.2	NR	23.4 $\pm$ 6.8	NR	NR
		Placebo	200 (89 / 111)	39.9 $\pm$ 9.7	NR	23.6 $\pm$ 7.6	NR	NR
Sachs (1993); <sup>68</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 18 years); smoked $\geq$ 10 cigarettes per day for $\geq$ 3 years <i>Exclusion:</i> Cardiovascular disease; diabetes; on psychotropic medication; pregnancy or lactation; skin diseases; allergy; substance abuse; use of other forms of nicotine	Nicotine patch	113 (46/67)	47.5 $\pm$ 10.7 (range: 24-69)	28.7 $\pm$ 10.5 (range: 5-51)	27.3 $\pm$ 9.5 (range: 10-60)	6.7 $\pm$ 1.7 (range 2-11)	5.5 $\pm$ 9.5 (range 1-99)
		Placebo	107 (44/63)	47.8 $\pm$ 10.8 (range: 25-71)	28.5 $\pm$ 11.1 (range: 6-50)	28.8 $\pm$ 11.1 (range: 10-70)	6.6 $\pm$ 1.7 (range 2-10)	4.7 $\pm$ 7.2 (range 1-50)

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
Stapleton (1995); <sup>74</sup> RCT, double-blind, parallel [same study as Russell (1993) <sup>73</sup> with full sample]	<i>Inclusion:</i> Motivated-to-quit smokers (age 20-60 years); smoked ≥15 cigarettes per day  <i>Exclusion:</i> Cardiovascular disease; hypertension; diabetes; on psychotropic medication; pregnancy or lactation; skin diseases; allergy; use of nicotine gum in the past 3 months	Nicotine patch	800 (335/465)	40.3 ± 9.9	NR	23.6 ± 6.9	NR	NR
		Placebo	400 (179/221)	41.5 ± 10.2	NR	24.2 ± 7.6	NR	NR
Tonnesen (1991, 1992); <sup>360,361</sup> Mikkelsen (1994); <sup>78</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥ 20 years); smoked ≥10 cigarettes per day for ≥3 years  <i>Exclusion:</i> Cardiovascular disease; pregnancy or lactation; use of psychotropic drugs; substance abuse; use of smokeless tobacco; skin disease	Nicotine patch	145 (45/100)	45.3 (range: 22-77)	25.9 (range: 5-57)	21 (range: 10-40)	7.1 (range: 3-11)	2.5 (range 0-10)
		Placebo	144 (42/102)	45.1 (range 23-77)	26.7 (range: 4-61)	22 (range: 10-40)	7.4 (range: 4-11)	2.8 (range 0-25)
Tonnesen (1999); <sup>80</sup> RCT, double-blind, parallel [CEASE]	<i>Inclusion:</i> Motivated-to-quit smokers (age 20-70 years); smoked ≥14 cigarettes per day for ≥3 years  <i>Exclusion:</i> Heart diseases; pregnancy or lactation; under psychiatric care or medication; substance abuse; skin diseases; cancer; participation in other smoking cessation programs; use of other forms of nicotine	25-mg nicotine patch, 22 wks	715 (372/343)	40 ± 10	NR	28 ± 11	5.6 ± 2.1	2.9±3.0
		25-mg nicotine patch, 8 wks	715 (379/336)	41 ± 10	NR	26 ± 9	5.6 ± 2.1	2.9±3.3
		15-mg nicotine patch, 22 wks	715 (372/343)	40 ± 10	NR	26 ± 10	5.6 ± 2.1	3.1±4.9
		15-mg nicotine patch, 8 wks	716 (365/351)	41 ± 10	NR	27 ± 10	5.4 ± 2.1	3.1±3.2
		Placebo	714 (371/343)	41 ± 10	NR	27 ± 10	5.6 ± 2.1	3.0±3.3
TNS group (1991, 1999); <sup>69,362</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers; smoked ≥1 pack of cigarettes per day for ≥1 year; had made at least one attempt to quit; CO level ≥10 ppm; generally healthy  <i>Exclusion:</i> Use of smokeless tobacco, pipes, cigars or nicotine gum; serious medical conditions; substance abuse	Nicotine patch (21 mg)	262 (106/156)	43.1 ± 10.4 (range: 22-66)	24.9 ± 10.4 (range: 1-50)	31.1 ± 10.5 (range: 12-90)	7.2 ± 1.7 (range: 2-11)	4.4±4.2 (range 1-30)
		Nicotine patch (14 mg)	275 (112/163)	42.5 ± 10.6 (range: 22-68)	24.0 ± 10.4 (range: 1-50)	31.0 ± 10.3 (range: 15-80)	7.0 ± 1.7 (range: 2-11)	4.1±4.4 (range 1-40)

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
		Nicotine patch (7 mg)	127 (54/73)	40.7 $\pm$ 9.8 (range: 23-65)	22.3 $\pm$ 9.1 (range: 6-48)	29.8 $\pm$ 8.4 (range: 20-50)	7.2 $\pm$ 1.7 (range: 3-11)	4.1 $\pm$ 5.4 (range 1-50)
		Placebo	271 (99/172)	43.2 $\pm$ 9.9 (range: 21-65)	24.2 $\pm$ 9.9 (range: 2-55)	30.5 $\pm$ 10.6 (range: 20-80)	7.1 $\pm$ 1.7 (range: 2-11)	3.8 $\pm$ 3.3 (range 1/20)
Westman (1993); <sup>70</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit and relatively healthy smokers (age 18-65 years); smoked $\geq$ 1 pack of cigarettes per day <i>Exclusion:</i> Skin allergy; psychiatric disorders; pregnancy	Nicotine patch	79 (34/45)	41.9 $\pm$ 8.5	22.5 $\pm$ 10.4	28.9 $\pm$ 10.6	6.6 $\pm$ 1.3	4.0 $\pm$ 3.9
		Placebo	80 (35/45)	41.7 $\pm$ 7.4	23.1 $\pm$ 7.5	30.8 $\pm$ 12.4	6.6 $\pm$ 2.0	3.4 $\pm$ 3.4
Wisborg (2000); <sup>79</sup> RCT, parallel	<i>Inclusion:</i> Healthy pregnant women; smoked $\geq$ 10 cigarettes per day; <22 wks pregnant <i>Exclusion:</i> NR	Nicotine patch	124 (0/124)	28.2 $\pm$ 4.9	NR	13.4 $\pm$ 4.0	NR	NR
		Placebo	126 (0/126)	28.5 $\pm$ 5.2	NR	14.2 $\pm$ 4.4	NR	NR
<b>Nicotine gum vs. placebo</b>								
Ahluwalia (2006); <sup>81</sup> RCT, double-blind, parallel	<i>Inclusion:</i> African American or black, motivated-to-quit and relatively healthy smokers (age $\geq$ 18 years); smoked $\leq$ 10 cigarettes per day for $\geq$ 6 months; working telephone <i>Exclusion:</i> Contraindication for nicotine gum; heart disease; use of other drug(s) for smoking cessation; pregnancy or lactation; inappropriate affect or behaviour	Nicotine gum + interview	189 (64/125)	45.2 $\pm$ 10.7	23.5 $\pm$ 12.1	7.8 $\pm$ 3.5	4.1 $\pm$ 2.16	2.8 $\pm$ 4.4 (in past year)
		Nicotine gum + education	189 (60/129)	43.5 $\pm$ 11.8	22.8 $\pm$ 12.8	7.5 $\pm$ 2.9	4.3 $\pm$ 2.0	2.8 $\pm$ 5.1 (in past year)
		Placebo + interview	189 (66/123)	46.5 $\pm$ 10.0	25.1 $\pm$ 11.4	7.5 $\pm$ 3.5	4.2 $\pm$ 2.2	4.0 $\pm$ 10.0 (in past year)
		Placebo + education	188 (60/128)	45.2 $\pm$ 10.0	24.2 $\pm$ 11.5	7.3 $\pm$ 2.8	4.5 $\pm$ 2.2	3.4 $\pm$ 5.6 (in past year)
Areechon (1988); <sup>99</sup> randomized,	<i>Inclusion:</i> Recruited healthy smokers (age <60 years); smoked $\geq$ 15 cigarettes per day	Nicotine gum	98 (92/6)	38	19.6	24.8	NR	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
parallel	<i>Exclusion:</i> NR	Placebo	101 (96/5)	40	20.6	23.8	NR	NR
Batra (2005); <sup>100</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Unwilling-to-quit smokers (age $\geq$ 18 years); smoked $\geq$ 20 cigarettes per day for $\geq$ 3 years; CO level $\geq$ 15 ppm; made at least 1 failed quit attempt within 2 years before the study, but not in the previous 6 months; difficult to achieve abstinence on their own  <i>Exclusion:</i> Intent to quit; current use of nicotine replacement therapy; cardiovascular disease; psychiatric disorders; substance abuse	Nicotine gum	184 (100/84)	42.6 $\pm$ 9.9	NR	27.9 $\pm$ 9.2	5.7 $\pm$ 1.8	NR
		Placebo	180 (117/63)	43.5 $\pm$ 10.3	NR	29.6 $\pm$ 9.5	5.9 $\pm$ 1.9	NR
Blondal (1989); <sup>101</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Daily smokers (age 25-74 years ) from a previous research group  <i>Exclusion:</i> NR	Nicotine gum	92 (41/51)	44	NR	NR	6.2	NR
		Placebo	90 (37/53)	40	NR	NR	5.7	NR
Clavel-Chapelon (1997); <sup>102</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age $\geq$ 18 years); smoked $\geq$ 10 cigarettes per day  <i>Exclusion:</i> Gastric ulcer; heart disease; dental problems; pregnancy or lactation	Nicotine gum	481 (265/216)	34	18 $\pm$ 9	NR	NR	NR
		Placebo	515 (283/232)				NR	NR
Cooper (2005); <sup>82</sup> RCT, parallel	<i>Inclusion:</i> Relatively healthy female smokers (age 18-70 years); smoked $\geq$ 10 cigarettes a day  <i>Exclusion:</i> Hypertension; pregnancy or lactation; depression; psychiatric disorders; heart disease; endocrine disorders; ulcers; kidney or liver disease; lung disease; substance abuse	Nicotine gum	146 (0/146)	38.4 $\pm$ 10.8	19.4 $\pm$ 9.7	$\geq$ 10	5.5 $\pm$ 2.1	NR
		Placebo	148 (0/148)	39.0 $\pm$ 10.2	19.5 $\pm$ 10.3	$\geq$ 10	5.8 $\pm$ 2.0	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Fagerström (1982); <sup>95</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers attending a smoking withdrawal clinic who were in generally good health; 13% with smoke-related diseases (claudication intermittens, angina pectoris, cardiac infarction and emphysema); 36% had minor disorders (bronchitis, gastritis, and Raynaud's disease)  <i>Exclusion:</i> NR	Nicotine gum	47 (NR/NR)	NR	NR	NR	NR	NR
		Placebo	49 (NR/NR)	NR	NR	NR	NR	NR
Fortmann (1988); <sup>83</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Recruited smokers (age 18-65 years)  <i>Exclusion:</i> Pregnancy or lactation; cancer or peptic ulcer disease; temporomandibular joint disease; those with heart disease, chest pain, diabetes, or thyroid disease needed permission from physicians	Nicotine gum	152 (74/78)	Range 18-65	25.5 $\pm$ 11.4	24.0 $\pm$ 12.3	NR	3.4 $\pm$ 1.9
		Placebo	148 (77/71)	Range 18-65	25.5 $\pm$ 10.4	26.0 $\pm$ 11.5	NR	3.5 $\pm$ 2.0
Garvey (2000); <sup>84</sup> RCT, parallel	<i>Inclusion:</i> Recruited smokers (age $\geq$ 20 years); smoked $\geq$ 5 cigarettes per day; adequate health; letter from physician stating no obvious medical conditions present  <i>Exclusion:</i> NR	Nicotine gum (2 mg)	202 (93/109)	41.0 $\pm$ 12.3	NR	23.3 $\pm$ 11.3	5.7 $\pm$ 2.3	NR
		Nicotine gum (4 mg)	203 (105/98)	41.4 $\pm$ 11.7	NR	23.9 $\pm$ 11.1	5.5 $\pm$ 2.2	NR
		Placebo	203 (98/105)	40.1 $\pm$ 11.6	NR	23.3 $\pm$ 11.1	5.4 $\pm$ 2.4	NR
Hall (1987); <sup>85</sup> RCT, parallel	<i>Inclusion:</i> Recruited smokers; physician's verification of health status; signed informed consent  <i>Exclusion:</i> NR	Nicotine gum	36 (NR/NR)	39	NR	30	NR	NR
		Placebo	34 (NR/NR)		NR		NR	
		Nicotine gum + behaviour	35 (NR/NR)		NR		NR	
		Placebo + behaviour	34 (NR/NR)		NR		NR	

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
Hall (1996); <sup>86</sup> RCT, parallel	<i>Inclusion:</i> Recruited smokers; physician's verification of health status  <i>Exclusion:</i> Pregnancy or lactation; heart disease, ulcers, oral thrush; substance abuse; use of psychoactive drug or mental health treatment	Nicotine gum	75 (NR/NR)	39.7	21	≥10	NR	NR
		Placebo	82 (NR/NR)				NR	NR
		Nicotine gum (depression)	23 (NR/NR)				NR	NR
		Placebo (depression)	21 (NR/NR)				NR	NR
Herrera (1995); <sup>103</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥20 years); smoked ≥10 cigarettes per day; scored ≥4 on FTQ  <i>Exclusion:</i> Heart disease, hypertension, peptic ulcer; diabetes; pregnancy or lactation; dental problem; use of psychotropic medications; substance abuse	High-dependent (2 or 4 mg)	168 (97/71)	39.7 ± 9.7	NR	33.4 ± 11.7	7.9 ± 1.0	NR
		Low-dependent (0 or 2 mg)	154 (86/68)	37.4 ± 8.7	NR	15.7 ± 5.1	5.3 ± 0.6	NR
Hjalmarson (1984); <sup>96</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers with smoking-related disorders (chronic bronchitis; emphysema, asthma, and cardiovascular disease)  <i>Exclusion:</i> Previous use of nicotine chewing gum; psychosis; mental retardation; substance abuse	Nicotine gum	106 (49/57)	42.8 ± 11.2	NR	23.9 ± 9.9	NR	NR
		Placebo	100 (41/59)	41.3 ± 13.6	NR	24.2 ± 10.3	NR	NR
Hughes (1989); <sup>87</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers from 2 family practice clinics; able to chew gum  <i>Exclusion:</i> Prior use of nicotine gum; use of other form of tobacco; contraindication with nicotine gum; pregnancy; temporomandibular joint disease	Nicotine gum	210 (95/115)	37.4 ± 9.7	19.7 ± 9.1	29.8 ± 10.7	5.7 ± 1.5	NR
		Placebo	105 (43/62)	36.3 ± 10.3	18.7 ± 10.2	29.2 ± 12.0	5.8 ± 1.5	NR
Jamrozik (1984); <sup>92</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers; recruited from 6 family practice clinics  <i>Exclusion:</i> Contraindications to use of nicotine gum	Nicotine gum	101 (NR/NR)	NR	NR	NR	NR	NR
		Placebo	99 (NR/NR)	NR	NR	NR	NR	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Jarvis (1982); <sup>93</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers; recruited from a hospital smokers' clinic <i>Exclusion:</i> NR	Nicotine gum	58 (29/29)	41	NR	30.9	NR	NR
		Placebo	58 (23/35)	38.4	NR	26.5	NR	NR
Kinnunen (2008); <sup>88</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq 20$ years); in good health; smoked $\geq 5$ cigarettes per day; letter from physician stating no obvious medical condition that would prevent participation to the study <i>Exclusion:</i> On psychiatric medications	Depressed (Nicotine gum and placebo)	196 (86/110)	38.5 $\pm$ 11.3	NR	23.5 $\pm$ 11.1	5.9 $\pm$ 2.3	NR
		Non-depressed (Nicotine gum and placebo)	412 (210/202)	41.9 $\pm$ 12.0	NR	23.6 $\pm$ 11.2	5.3 $\pm$ 2.2	NR
Malcolm (1983); <sup>94</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Recruited smokers or referred by family physicians <i>Exclusion:</i> NR	Nicotine gum	73 (44/29)	44 (range: 16-72)	NR	25.6 (range: 5-70)	NR	NR
		Placebo	63 (36/27)	45 (range: 18-65)	NR	26.3 (range: 5-60)	NR	NR
Oncken (2008); <sup>89</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Pregnant women (age $\geq 16$ years); smoked $\geq 1$ cigarette per day; at $\leq 26$ wks of gestation; spoke English or Spanish; intended to carry the pregnancy to term; lived in a stable residence <i>Exclusion:</i> Substance abuse; twins or other multiple gestation; unstable psychiatric problem; unstable medical problem; high-risk pregnancy	Nicotine gum	100 (0/100)	25.5 $\pm$ 6.8 (gestational age: 17.1 $\pm$ 5.6 wks)	NR	10.2 $\pm$ 6.6	3.8 $\pm$ 1.9	3.03 $\pm$ 5.69
		Placebo	94 (0/94)	24.7 $\pm$ 5.4 (gestational age: 17.1 $\pm$ 5.5 wks)	NR	8.7 $\pm$ 5.7	3.6 $\pm$ 2.0	2.55 $\pm$ 5.66
Schneider (1983); <sup>90</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers recruited through advertisement; smoked $\geq 1$ pack of cigarettes per day <i>Exclusion:</i> Ill health; use of prescription drugs or birth control pills; pregnancy	Nicotine gum	43	NR	NR	NR	NR	NR
		Placebo	53	NR	NR	NR	NR	NR
Shiffman (2009); <sup>91</sup>	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq 18$ years); interest in using gradual	Nicotine gum (2 mg)	819 (305/514)	42.1 $\pm$ 13.0	24.1 $\pm$ 12.8	17.7 $\pm$ 6.0	4.4 $\pm$ 2.1	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
RCT, double-blind, parallel	reduction within 30 days; understanding of English; provision of written informed consent  <i>Exclusion:</i> Use of other forms of nicotine; heart disease; diabetes; involvement in another clinical study; being in the same household with another participant; relation to study site staff; working during night hours; pregnancy or lactation	Placebo	817 (282/535)	42.2 $\pm$ 13.3	24.3 $\pm$ 13.6	17.6 $\pm$ 6.1	4.4 $\pm$ 2.1	NR
		Nicotine gum (4 mg)	830 (435/395)	46.1 $\pm$ 11.3	29.2 $\pm$ 11.3	32.0 $\pm$ 9.6	6.9 $\pm$ 1.7	NR
		Placebo	831 (397/434)	46.3 $\pm$ 11.4	29.5 $\pm$ 11.7	32.5 $\pm$ 10.0	6.9 $\pm$ 1.7	NR
Tonnesen (1988); <sup>98</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 17 years); smoked $\geq$ 10 cigarettes per day  <i>Exclusion:</i> Peptic ulcer; substance abuse; psychiatric disorders; pregnancy	High-dependence (4 mg)	27 (12/15)	46.6 $\pm$ 9.9	NR	25.8 $\pm$ 7.6	NR	NR
		High-dependence (2 mg)	33 (13/20)	44.7 $\pm$ 10.9	NR	28.3 $\pm$ 9.2	NR	NR
		Low-dependence (2 mg)	60 (28/32)	44.9 $\pm$ 10.4	NR	20.3 $\pm$ 7.7	NR	NR
		Low-dependence (placebo)	53 (22/31)	45.5 $\pm$ 11.7	NR	19.3 $\pm$ 5.5	NR	NR
Wennike (2003); <sup>97</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers (age $\geq$ 18 years); smoked $\geq$ 15 cigarettes per day for $\geq$ 3 years; exhaled CO levels $\geq$ 15 ppm; failed at least one serious quit attempt within the last 2 years  <i>Exclusion:</i> Current use of NRT or pharmacological smoking cessation/reduction program; use other forms of nicotine products; heart disease; psychiatric disorders; substance abuse	Nicotine gum	205 (72/133)	45 $\pm$ 10	28.0 $\pm$ 9.9	24 $\pm$ 7	6.4 $\pm$ 1.9	NR
		Placebo	206 (84/122)	44 $\pm$ 10	27.9 $\pm$ 9.0	24 $\pm$ 7	6.4 $\pm$ 1.8	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
<b>Nicotine lozenge vs. placebo</b>								
Shiffman (2002, 2005); <sup>104,363,383</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥18 years)  <i>Exclusion:</i> Use of other smoking cessation aids or other forms of nicotine or tobacco during the past 30 days; pregnancy; heart disease; stomach ulcer; hypertension; diabetes; experience problems with aspartame	Low-dependence (active, 2-mg)	459 (197/262)	41.11 ± 12.06	NR	17.7 ± 8.2	2.6 ± 1.8	4.0±6.0
		Low-dependence (placebo)	458 (184/274)	40.48 ± 11.94	NR	17.2 ± 9.4	2.6 ± 1.9	5.1±9.8
		High-dependence (active, 4-mg)	450 (195/255)	44.28 ± 11.78	NR	26.3 ± 11.2	6.1 ± 1.8	3.9±4.3
		High-dependence (placebo)	451 (212/239)	44.51 ± 11.92	NR	26.9 ± 10.1	6.2 ± 1.8	4.4±8.2
<b>Nicotine sublingual vs. placebo</b>								
Glover (2002), <sup>105</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥20 years); smoked ≥10 cigarettes per day for the last 3 years; in general good health; CO levels ≥10 ppm  <i>Exclusion:</i> Cardiovascular disease; oral mucosal disorder; pregnancy or lactation; use of psychotropic medication; use of other form of tobacco; use of NRT in the previous 6 months	Nicotine sublingual	120 (57/63)	43.9 ± 10.0	25.8 ± 10.4	28.5 ± 11.5	7.0 ± 1.8	NR
		Placebo	121 (54/67)	41.8 ± 11.6	24.2 ± 11.3	29.4 ± 10.5	7.1 ± 1.7	NR
Tonnesen (2006); <sup>106</sup> RCT, double-blind, parallel	<i>Inclusion:</i> COPD patients (age ≥18 years) recruited from lung clinics; smoked ≥1 cigarette per day; had persistent airway obstruction with FEV <sub>1</sub> /FVC <70% and FEV <sub>1</sub> < 90%  <i>Exclusion:</i> Use of another form of smoking cessation therapy; predicted survival <1 year; unable to adhere the protocol	Nicotine sublingual + low support	95 (45/50)	59.2 ± 10.3	NR	20.1 ± 10.7	6.0 ± 2.1	2.7±3.4
		Placebo + low support	88 (40/48)	62.5 ± 9.3	NR	20.2 ± 9.6	6.1 ± 1.9	2.1±2.3
		Nicotine sublingual + high support	90 (46/44)	61.3 ± 9.6	NR	18.3 ± 10.4	5.9 ± 2.2	2.2±2.3

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
		Placebo + high support	97 (46/51)	61.2 ± 9.4	NR	19.9 ± 8.8	6.4 ± 1.8	3.3±6.3
Wallstrom (2000); <sup>107</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Healthy male and female smokers (age ≥20 years); smoked ≥10 cigarettes per day for the last 3 years; CO levels ≥10 ppm  <i>Exclusion:</i> Mouth disease; cardiovascular disease; use of psychotropic medication; use of other forms of tobacco or other NRT products during the last 6 months; pregnancy or lactation	Nicotine sublingual	123 (45/78)	44.5 ± 11.6	26.1 ± 10.3	18.2 ± 5.4	6.3 ± 1.8	NR
		Placebo	124 (56/68)	44.7 ± 11.4	26.9 ± 9.8	20.6 ± 6.8	7.1 ± 1.8	NR
<b>Oral nicotine inhaler vs. placebo</b>								
Bolliger (2000); <sup>108</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers (age ≥18 years); smoked ≥15 cigarettes per day for ≥3 years; CO levels ≥10 ppm; failed at least one serious attempt to quit within the past 12 months; desire to reduce smoking as much as possible with the help of nicotine inhaler  <i>Exclusion:</i> Current use of NRT or other behavioural or pharmacological smoking cessation or reduction program; use of products containing nicotine	Nicotine inhaler	200 (86/114)	46.4 ± 10.5 (range: 23-79)	NR	28.2 ± 11.4 (range: 15-70)	5.5 ± 2.1 (range: 1-10)	NR
		Placebo	200 (104/96)	45.8 ± 10.5 (range: 22-77)	NR	30.3 ± 12.1 (range: 15-70)	5.6 ± 2.0 (range: 1-10)	NR
Hjalmarson (1997); <sup>109</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers (age ≥20 years); smoked ≥10 cigarettes per day for ≥3 years; previous serious quit attempt using nicotine gum  <i>Exclusion:</i> Severe cardiovascular disease; pregnancy or lactation; current use of psychotropic drugs, substance abuse; current use of other forms of tobacco; use of NRT during the last 12 months; acute medical illness	Nicotine inhaler	123 (47/76)	48.0 ± 10.6	30.0 ± 10.3	21.7 ± 8.1	7.3 ± 1.9	NR
		Placebo	124 (42/82)	47.0 ± 9.5	28.9 ± 8.7	21.0 ± 7.8	7.0 ± 1.8	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Rennard (2006); <sup>110</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers (age $\geq$ 18 years); smoked $\geq$ 20 cigarettes per day for $\geq$ 3 years; CO levels $\geq$ 15 ppm; failed at least one serious attempt to quit within the past 2 years; desire to reduce smoking  <i>Exclusion:</i> Plan to quit smoking within the next 4 wks; current use of NRT or other behavioural or pharmacological smoking cessation or reduction program; use of products containing nicotine; heart disease; pregnancy or lactation; use of psychiatric medications; substance abuse	Nicotine inhaler	215 (88/127)	45.9 $\pm$ 12.3	NR	29.3 $\pm$ 10.1	6.5 $\pm$ 2.0	NR
		Placebo	214 (104/110)	44.8 $\pm$ 12.1	NR	30.4 $\pm$ 9.9	6.6 $\pm$ 1.9	NR
Schneider (1996); <sup>111</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers smoked $\geq$ 10 cigarettes per day for $\geq$ 3 years  <i>Exclusion:</i> Acute or chronic medical conditions; psychiatric conditions; substance abuse; use of transdermal nicotine patch in the previous year	Nicotine inhaler	112 (72/40)	43.7 $\pm$ 11.3	25.3 $\pm$ 11.2	29.2 $\pm$ 11.3	7.5 $\pm$ 1.5	NR
		Placebo	111 (69/42)	44.4 $\pm$ 10.8	26.1 $\pm$ 10.8	26.2 $\pm$ 9.8	7.2 $\pm$ 1.7	NR
Tonnesen (1993); <sup>112</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 20 years); smoked $\geq$ 10 cigarettes per day for $\geq$ 3 years  <i>Exclusion:</i> Cardiovascular disease; severe asthma; COPD; pregnancy or lactation; use of psychotropic drugs; use of other forms of tobacco; substance abuse; receipt of NRT within the past 6 months	Nicotine inhaler	145 (61/84)	39 $\pm$ 12	21 $\pm$ 10	20 $\pm$ 6	7.4 $\pm$ 1.7	2.4 $\pm$ 9.8
		Placebo	141 (52/89)	39 $\pm$ 14	20 $\pm$ 11	20 $\pm$ 7	7.3 $\pm$ 1.7	1.4 $\pm$ 2.3
<b>Nicotine nasal spray vs. placebo</b>								
Blondal (1997); <sup>113</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 21-68 years); smoked $\geq$ 1 cigarettes per day  <i>Exclusion:</i> Heart disease; substance abuse; pregnancy or lactation	Nicotine spray	79 (40/39)	42 (range: 22-67)	2.7 (range: 1-5)	26 (range: 4-50)	7.1 (range: 3-10)	NR
		Placebo	78 (30/48)	42 (range: 21-67)	2.7 (range: 1-5)	24 (range: 6-45)	7.3 (range: 4-10)	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
Hjalmarson (1994); <sup>114</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 21-68 years)  <i>Exclusion:</i> Severe cardiovascular disease; pregnancy or lactation; chronic disorder of nose; use of other forms of tobacco; use of psychotropic medication; substance abuse	Nicotine spray	125 (53/72)	44.9 ± 11.5	26.9 ± 10.3	21.2 ± 5.9	NR	NR
		Placebo	123 (53/70)	44.9 ± 11.1	26.6 ± 9.9	21.6 ± 8.3	NR	NR
Schneider (1995); <sup>115</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers, smoked ≥15 cigarettes per day for ≥2 years; baseline CO level ≥20 ppm  <i>Exclusion:</i> Acute or chronic medical conditions; use of psychoactive medication; substance abuse; psychiatric disorders; nasal problems (allergic and sinus conditions)	Nicotine spray	128 (66/62)	39.9 ± 7.7	22.8 ± 8.4	28.8 ± 10.9	NR	NR
		Placebo	127 (74/53)	39.7 ± 7.2	21.8 ± 7.7	28.6 ± 9.9	NR	NR
Sutherland (1992); <sup>116</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 18-68 years), in good health  <i>Exclusion:</i> Cardiovascular disease; hypertension; diabetes; severe allergy; use of psychotropic medication; use of nicotine gum in the past year; substance abuse; pregnancy	Nicotine spray	116 (43/73)	38.9 ± 9.4	21.6 ± 9.8	24.9 ± 10.4	NR	NR
		Placebo	111 (38/73)	40.4 ± 9.9	23.5 ± 10.2	26.9 ± 9.6	NR	NR
<b>Nicotine patch vs. nicotine spray</b>								
Croghan (2003); <sup>117</sup> RCT, open-label, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥18 years); smoked ≥15 cigarettes per day for the past year; generally good health  <i>Exclusion:</i> Heart disease; other medical conditions that are deemed incompatible with study participation; psychiatric disorders; use of psychiatric drugs; nasal problems, allergies, sinusitis; pregnancy or lactation; current use of other tobacco products, NRT, or other pharmacotherapy on smoking cessation; skin disease	Nicotine patch alone	459 (58% female overall)	42 ± 10.8	23.3 ± 10.7	26.2 ± 9.8	NR	NR
		Nicotine spray alone	463 (58% female overall)				NR	NR
		Combined patch and spray	462 (58% female overall)				NR	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Lerman (2004); <sup>118</sup> RCT, open-label, parallel	<i>Inclusion:</i> Smokers (age $\geq$ 18 years); smoked $\geq$ 10 cigarettes per day for the past year  <i>Exclusion:</i> Pregnancy or lactation; uncontrolled hypertension; heart disease; cancer; substance abuse; psychotic disorder; use of bupropion; use of other nicotine-containing products	Nicotine patch	144 (73/71)	46 $\pm$ 11	NR	21 $\pm$ 11	NR	NR
		Nicotine spray	155 (64/91)		NR		NR	NR
<b>Nicotine patch vs. nicotine gum vs. placebo</b>								
Moolchan (2005); <sup>119</sup> RCT, double-blind, double-dummy, parallel	<i>Inclusion:</i> Adolescent smokers (age 13-17 years) desiring to quit; ability to discuss their smoking with parents/guardians; general good health; FTND $\geq$ 5; smoke $\geq$ 10 cigarettes/d for $\geq$ 6 months  <i>Exclusion:</i> Major physical health problems; untreated acute psychiatric problems; pregnancy or lactation; skin disease; use of other tobacco products; current use of medications for smoking cessation; substance abuse	Nicotine patch + placebo gum	34 (13/21)	15.4 $\pm$ 1.41	2.57 $\pm$ 1.29	17.7 $\pm$ 6.45	7.00 $\pm$ 1.11	NR
		Nicotine gum + placebo patch	46 (14/32)	15.0 $\pm$ 1.31	2.73 $\pm$ 1.88	18.9 $\pm$ 8.96	7.09 $\pm$ 1.39	NR
		Placebo gum + placebo patch	40 (9/31)	15.2 $\pm$ 1.29	2.66 $\pm$ 1.35	19.6 $\pm$ 9.70	7.00 $\pm$ 1.32	NR
<b>Nicotine lozenge vs. nicotine gum</b>								
Pack (2008), <sup>120</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 18 years); smoked $\geq$ 10 cigarettes per day for the past 6 months; CO levels of $\geq$ 10 ppm  <i>Exclusion:</i> Current use of another smoking cessation medication; contraindication to use of nicotine gum or lozenge; unstable cardiovascular disease; mental illness; pregnancy	Lozenge + Quit line	104 (45/59)	43.4 $\pm$ 12.7	26.5 $\pm$ 12.2	23.8 $\pm$ 10.2	5.9 $\pm$ 2.2	3.4 $\pm$ 2.5
		Gum + Quit line	101 (45/56)	40.0 $\pm$ 12.0	23.5 $\pm$ 11.6	22.3 $\pm$ 9.8	5.7 $\pm$ 2.3	4.2 $\pm$ 5.0
		Lozenge + Self help	101 (45/56)	43.2 $\pm$ 13.1	26.0 $\pm$ 12.6	23.3 $\pm$ 9.9	6.2 $\pm$ 2.1	4.4 $\pm$ 3.8
		Gum + Self help	102 (44/58)	43.6 $\pm$ 10.9	27.1 $\pm$ 11.2	22.9 $\pm$ 9.6	6.1 $\pm$ 2.1	3.9 $\pm$ 3.4

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
<b>Nicotine patch vs. nicotine inhaler</b>								
Tønnesen (2000); <sup>121</sup> RCT, open-label, parallel	<i>Inclusion:</i> Smokers referred to lung clinic (age 20-70 years); motivated -to-quit; smoked ≥10 cigarettes per day; willingness to use NRT  <i>Exclusion:</i> Suspicion of lung cancer or tuberculosis; senile subjects; non-cooperative subjects; pregnancy or lactation	5-mg nicotine patch	109 (55/54)	49 ± 13	NR	18.8 ± 7.3	NR	NR
		15-mg nicotine patch	104 (48/56)	50 ± 12	NR	18.1 ± 5.5	NR	NR
		Nicotine inhaler	118 (54/64)	48 ± 10	NR	18.1 ± 6.8	NR	NR
		Inhaler + 15-mg patch	115 (49/66)	50 ± 13	Nr	19.3 ± 7.5	NR	NR
<b>Nicotine mouth spray vs. nicotine gum vs. oral nicotine inhaler</b>								
Bolliger (2007); <sup>122</sup> RCT, open-label, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥18 years); smoked >15 cigarettes per day for ≥3 years; CO levels >10 ppm; serious cessation attempt within the last 12 months  <i>Exclusion:</i> Current use of NRT; use of non-cigarette tobacco products; pregnancy or lactation; heart disease; major medical diseases; psychiatric disorders; cancer; use of psychoactive drugs; substance abuse	Nicotine mouth spray	50 (26/24)	42.5 ± 10.9	NR	23.0 ± 8.8	5.3 ± 2.2	NR
		Nicotine gum	25 (18/7)	43.0 ± 11.3	NR	23.7 ± 6.8	6.0 ± 1.9	NR
		Nicotine oral inhaler	25 (16/9)	44.3 ± 12.2	NR	23.9 ± 8.2	5.8 ± 1.9	NR
<b>Nicotine patch vs. nicotine patch + behaviour support</b>								
Alterman (2001); <sup>123</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age 21-65 years), smoked ≥1 pack of cigarettes per day; reported at least one previous failed attempt at smoking cessation  <i>Exclusion:</i> Severe medical conditions; psychiatric disorders; substance abuse	Patch + low intensity	80 (41/39)	40.9 ± 9.2	22.6 ± 9.7	27.3 ± 10.6	6.8 ± 1.5	6.3 ± 8.5
		Patch + middle intensity	80 (44/36)	40.1 ± 10.6	22.0 ± 10.4	27.2 ± 9.5	6.9 ± 1.6	4.5 ± 5.7
		Patch + high intensity	80 (37/43)	39.6 ± 8.9	20.9 ± 8.9	26.3 ± 9.8	6.9 ± 1.4	5.9 ± 7.0
Bock (2008); <sup>124</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age ≥18 years); admitted to the observation unit with chest pain; smoked ≥5 cigarettes/day for the past 3 months; willingness to participate in the study  <i>Exclusion:</i> Current use of smokeless tobacco, NRT or other smoking cessation treatment	Patch + usual care	272 (144/128)	47.7 ± 11.2	NR	18.9 ± 12.6	5.0 ± 2.5	NR
		Patch + behavioural support	271 (143/128)		NR			NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Lando (1997); <sup>125</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 18-65 years); smoked $\geq 20$ cigarettes per day for $\geq 2$ years  <i>Exclusion:</i> Heart disease; cardiovascular disease; skin allergy; psychiatric disorders; substance abuse; use of systemic steroids or antihistamines; pregnancy or lactation; current use of alternative NRT	Patch	174 (93/81)	41.3	23.4	27.6	5.2	6.1
		Path + help line	173 (67/106)	42.9	23.7	28.5	5.1	5.1
		Patch + help line + telephone counselling	162 (64/98)	41.6	23.2	27.4	5.0	5.2
Lifrak (1997); <sup>126</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age 21-65 years); smoked $\geq 1$ pack of cigarettes per day for at least the past month; at least one failed attempt at smoking cessation  <i>Exclusion:</i> Pregnancy or lactation; cardiovascular disease; allergies; severe hypertension; mental disorders; substance abuse	Patch + moderate intensity	36 (17/19)	38.9 $\pm$ 9.6	20.7 $\pm$ 8.2	25.3 $\pm$ 9.7	7.0 $\pm$ 1.6	3.5 $\pm$ 3.1
		Patch + high intensity	33 (10/23)	39.4 $\pm$ 10.3	21.8 $\pm$ 9.1	25.0 $\pm$ 10.0	7.5 $\pm$ 1.7	4.1 $\pm$ 4.3
Simon (2003); <sup>127</sup> RCT, parallel	<i>Inclusion:</i> Current smokers ( $\geq 20$ cigarettes per day during pre-hospitalization week); co-morbidities (cardiovascular disease, COPD, diabetes, hypertension, substance abuse, history of tobacco-related cancer, depression)  <i>Exclusion:</i> Patients hospitalized for psychiatric or terminal illness; contraindication to NRT	Patch + minimal counselling	116 (112/4)	54 $\pm$ 11	NR	24 $\pm$ 14	4 $\pm$ 2	NR
		Patch + intense counselling	107 (105/2)	55 $\pm$ 11	NR	23 $\pm$ 12	4 $\pm$ 2	NR
Solomon (2000); <sup>128</sup> RCT, parallel	<i>Inclusion:</i> Low-income women smokers (age 18-50 years); smoked $>4$ cigarettes/day; high intention to quit	Patch only	108 (0/108)	33.2 $\pm$ 9.1	NR	24.3 $\pm$ 11.5	5.6 $\pm$ 2.3	1.4 $\pm$ 1.6 (in past year)

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	smoking <i>Exclusion:</i> Current use of NRT; high income; history of heart disease; plan to move within 6 months; pregnancy or lactation	Patch + telephone support	106 (0/106)	32.9 $\pm$ 8.0	NR	23.0 $\pm$ 12.0	5.7 $\pm$ 2.3	1.6 $\pm$ 1.7 (in past year)
Stein (2006); <sup>129</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age $\geq$ 18 years) enrolled in methadone maintenance treatment program; smoked $\geq$ 10 cigarettes/day for the past 3 months; did not have to agree to try quit smoking or to use nicotine patch <i>Exclusion:</i> NR	Patch + brief advice	192 (104/88)	40.3 $\pm$ 8.6	NR	27.2 $\pm$ 10.9	NR	NR
		Patch + behavioural counselling (max)	191 (99/92)	39.9 $\pm$ 8.3	NR	26.3 $\pm$ 13.3	NR	NR
Wiggers (2006); <sup>130</sup> RCT, parallel	<i>Inclusion:</i> Patients in the outpatient department of vascular surgery, cardiology and vascular medicine of a medical centre; smokers (age $\geq$ 18 years) smoked $\geq$ 5 cigarettes/day; suffering from documented peripheral arterial disease or coronary artery disease <i>Exclusion:</i> Acute myocardial infarction in the previous month; unstable angina; serious arrhythmia; recent stroke; skin allergy; pregnancy	Patch alone	186 (115/71)	58 $\pm$ 12	NR	21 $\pm$ 10	NR	NR
		Patch + behavioural support	186 (118/68)	59 $\pm$ 12	NR	21 $\pm$ 10	NR	NR
<b>Nicotine gum vs. nicotine gum + behaviour</b>								
Fortmann (1995); <sup>131</sup> RCT, parallel	<i>Inclusion:</i> Smokers recruited by telephone (age 18-65 years) <i>Exclusion:</i> Pregnancy or lactation; cancer or peptic ulcer disease; temporomandibular joint disease; those with heart disease, thyroid disease, chest pain, or diabetes needed written permission from their physicians	Gum only	262 (152/110)	40.6 $\pm$ 10.8	NR	20.1 $\pm$ 10.3	NR	NR
		Gum + self-help program	260 (151/109)	39.3 $\pm$ 10.6	NR	20.1 $\pm$ 10.3	NR	NR
		Self-help program only	261 (151/110)	39.9 $\pm$ 10.4	NR	20.1 $\pm$ 10.5	NR	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Ginsberg (1992); <sup>132</sup> RCT, parallel	<i>Inclusion:</i> Smokers with physician's verification of health status <i>Exclusion:</i> Pregnancy; ulcers; serious cardiovascular disease	Gum only	35	38.2	NR	25.6	NR	NR
		Gum + psychological treatment (PT)	33		NR		NR	NR
		Gum + PT + partner support	31		NR		NR	NR
Hall (1985); <sup>133</sup> RCT, parallel	<i>Inclusion:</i> Smokers with physician's verification of health status; informed consent <i>Exclusion:</i> NR	Gum only	42	38	NR	30.5	NR	NR
		Gum + behavioural treatment	35		NR		NR	NR
		Behavioural treatment only	36		NR		NR	NR
Hall (1987); <sup>85</sup> RCT, parallel  (same study in gum vs. placebo)	<i>Inclusion:</i> Recruited smokers; physician's verification of health status; signed informed consent <i>Exclusion:</i> NR	Nicotine gum	36 (NR/NR)	39	NR	30	NR	NR
		Placebo	34 (NR/NR)		NR		NR	NR
		Nicotine gum + behaviour	35 (NR/NR)		NR		NR	NR
		Placebo + behaviour	34 (NR/NR)		NR		NR	NR
Killen (1984); <sup>134</sup> RCT, parallel	<i>Inclusion:</i> Recruited smokers <i>Exclusion:</i> NR	Gum only	22	44.1 $\pm$ 12.3	23.8 $\pm$ 10.4	31.7	6.9 $\pm$ 2.4	NR
		Gum + skills training	22					NR
		Skills training	20					NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
<b>NRT and/or bupropion + behaviour vs. usual care</b>								
Baker (2006); <sup>135</sup> RCT, parallel	<i>Inclusion:</i> Smokers with psychotic disorder (age $\geq$ 18 years); smoked $\geq$ 15 cigarettes/day  <i>Exclusion:</i> Medical conditions precluding the use of nicotine patches; acute psychosis; acquired cognitive impairment	Nicotine patch + behaviour	151	NR	NR	NR	NR	NR
		Usual care	147	NR	NR	NR	NR	NR
Lacasse (2008); <sup>141</sup> RCT, parallel	<i>Inclusion:</i> Hospitalized patients (heart and lung disease); current smokers (age $\leq$ 70 years); in the contemplation, preparation, or action stage of change  <i>Exclusion:</i> Refusal to participate; in the precontemplation stage of change; hospitalization for substance abuse; other disorder with a severe short-term prognosis	Nicotine patch + behaviour	99 (63/36)	52 $\pm$ 9	NR	20.4 $\pm$ 12.6	5.1 $\pm$ 2.2	2.4 $\pm$ 2.2
		Usual care	97 (66/31)	52 $\pm$ 10	NR	22.8 $\pm$ 9.4	5.5 $\pm$ 2.2	2.0 $\pm$ 2.2
Lewis (1998); <sup>66</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit hospitalized inpatient smokers ( $\geq$ 18 years); smoked $\geq$ 10 cigarettes/day; medical appropriateness for nicotine patch treatment  <i>Exclusion:</i> Substance abuse; psychiatric illness; pregnancy or lactation; use of other forms of nicotine products; skin disorders; discharged within 24 h of admission; admission to intensive care unit; heart disease	Nicotine patch + Counselling	62 (35/27)	43.4 $\pm$ 13.6	26.3 $\pm$ 13.4	24.0 $\pm$ 17.5	6.6 $\pm$ 2.1	NR
		Minimal care	61 (35/26)	43.0 $\pm$ 11.6	25.4 $\pm$ 12.7	22.5 $\pm$ 10.6	6.6 $\pm$ 1.9	NR
Mohiuddin (2007); <sup>138</sup> RCT, parallel	<i>Inclusion:</i> Hospitalized patients (cardiovascular disease); current smokers (age 30-75 years); smoked $\geq$ 5 years; FTND scores $>$ 7  <i>Exclusion:</i> Current substance abuse	NRT and/or bupropion + behaviour	109 (75/34)	54.0 $\pm$ 11.1	33 $\pm$ 12	26 $\pm$ 14	$>$ 7	NR
		Usual care	100 (56/44)	55.5 $\pm$ 10.8	34 $\pm$ 11	22 $\pm$ 12	$>$ 7	NR
Molyneux (2003); <sup>142</sup> RCT, parallel	<i>Inclusion:</i> Medical/surgery inpatients; smokers (age $\geq$ 18 years)	NRT + counselling	91 (58/33)	49.3 $\pm$ 15.9	33.1 $\pm$ 16.6	Median: 20 (range 3-80)	5 (range 3-6)	NR
		Usual care	92	51.0 $\pm$ 15.8	35.4 $\pm$	Median: 15	5 (range	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	<i>Exclusion:</i> Pregnancy or lactation; psychiatric patient; substance abuse; terminal illness; hypersensitivity to nicotine or menthol		(54/38)		16.0	(range 1-60)	3-6)	
Nagle (2005); <sup>136</sup> RCT, parallel	<i>Inclusion:</i> Hospitalized patients (age 18-80 years); admitted to the hospital for at least 24 h during a one-year period; smokers at some point in last 12 months  <i>Exclusion:</i> Patients involved in an accident, or in emergency department, day surgery, dialysis unit, transplant unit, or intensive care unit	NRT + nurse-provided intervention	711 (281/430)	Range 18-80	NR	NR	NR	NR
		Usual care	711 (236/475)	Range 18-80	NR	NR	NR	NR
Reid (2008); <sup>139</sup> RCT, parallel	<i>Inclusion:</i> Patients with drug or alcohol dependence; smoked $\geq 10$ cigarettes/day; interest in quitting smoking; enrollment in substance abuse program for $\geq 30$ days; medically and psychiatrically stable  <i>Exclusion:</i> NR	Nicotine patch + counselling	153 (78/75)	41.6 $\pm$ 10.2	25.2 $\pm$ 11.4	22.3 $\pm$ 11.6	5.9 $\pm$ 2.1	5.2 $\pm$ 11.9
		Usual care	72 (38/34)	41.0 $\pm$ 8.6	24.3 $\pm$ 10.0	21.6 $\pm$ 10.2	6.0 $\pm$ 1.8	4.9 $\pm$ 12.3
Rodríguez-Artalejo (2003); <sup>143</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 18-63 years); smoked during the preceding month; CO levels $>10$ ppm at the annual medical check up  <i>Exclusion:</i> Hypersensitivity to NRT; chronic dermatitis; cardiovascular and heart diseases; mental disorders; diabetes; hyperthyroidism; pregnancy or lactation; NRT use in the preceding 3 months; substance abuse	Patch + counselling	115 (100/15)	43.1 $\pm$ 8.2	26.9 $\pm$ 8.6	25.0 $\pm$ 10.6	4.5 $\pm$ 2.4	NR
		Control	103 (88/15)	43.3 $\pm$ 8.3	26.6 $\pm$ 8.6	27.6 $\pm$ 11.7	5.1 $\pm$ 2.8	NR
Simon (1997); <sup>140</sup> RCT, parallel	<i>Inclusion:</i> Patients hospitalized for non-cardiac surgery; either at the contemplation or action stage of quitting  <i>Exclusion:</i> Unlikeliness to leave hospital	Gum or patch + behaviour	168 (98% men overall)	54 $\pm$ 12	NR	19 $\pm$ 12	3.8 $\pm$ 1.9	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	postoperatively; contraindication to NRT (unstable angina or myocardial infarction); terminal illness							
Wakefield (2004); <sup>137</sup> RCT, parallel	<i>Inclusion:</i> Diagnosis of cancer; smoke tobacco more than weekly; ability to give consent; prognosis >6 months  <i>Exclusion:</i> NR	NRT + counselling	74 (48/26)	52.6 $\pm$ 13.8	37.4 $\pm$ 14.1	21.7 $\pm$ 12.1	NR	1.8 $\pm$ 1.8 (in past year)
		Control	63 (37/26)	51.9 $\pm$ 11.5	36.0 $\pm$ 12.8	21.4 $\pm$ 10.9	NR	1.0 $\pm$ 2.0 (in past year)
<b>NRT + behaviour vs. behaviour</b>								
Cinciripini (1996); <sup>145</sup> RCT, parallel	<i>Inclusion:</i> 3-year smoking history; smoked $\geq$ 15 cigarettes/day  <i>Exclusion:</i> Current cessation treatment; psychiatric disorder; uncontrolled systemic illness	Nicotine patch + behaviour	32 (7/25)	43.9 $\pm$ 9.9	23.8 $\pm$ 11.9	22.1 $\pm$ 9.2	6.1 $\pm$ 1.5	1.4 $\pm$ 1.5
		Behaviour only	32 (12/20)	49.9 $\pm$ 11.0	26.9 $\pm$ 11.0	28.9 $\pm$ 13.7	5.9 $\pm$ 1.8	1.8 $\pm$ 1.4
Gilbert (1989); <sup>154</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age 16-65 years); smoked $\geq$ 1 cigarettes/day  <i>Exclusion:</i> Pregnancy or lactation	Nicotine gum + intervention support	112 (NR/NR)	NR	NR	NR	NR	NR
		Intervention support	111 (NR/NR)	NR	NR	NR	NR	NR
Hand (2002); <sup>155</sup> RCT, parallel	<i>Inclusion:</i> Hospital inpatients or outpatients with smoking related disease (age $\geq$ 18 years) referred to counsellor by hospital doctor  <i>Exclusion:</i> Substance abuse; active psychiatric illness; pregnancy or lactation; myocardial infarction during the last month	NRT + advice & support	136 (57/79)	$\geq$ 18 years	NR	$\geq$ 1	NR	NR
		Advice & support alone	109 (55/54)		NR		NR	NR
Harackiewicz (1988); <sup>146</sup> RCT, parallel	<i>Inclusion:</i> Patients and staff of a university centre and a university campus health service	Nicotine gum + self-help manual	99	Range 18-76	17	26.5 (range: 10-75)	NR	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	<i>Exclusion:</i> Recent myocardial infarction; unstable angina pectoris; hypertension; peripheral vascular disease; ulcers; pregnancy or lactation; difficulty in chewing; mouth sores; temporomandibular joint disease; dental infection; hemodialysis; hepatitis	Self-help manual	52				NR	NR
		Short booklet	46				NR	NR
Hill (1993); <sup>147</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age $\geq$ 50 years), smoked $\geq$ 30 years  <i>Exclusion:</i> Physical and/or psychological impairment	Nicotine Gum + behaviour	22 (NR/NR)	59.4 $\pm$ 7.2	39.8 $\pm$ 8.9	27.8 $\pm$ 13.6	6.5 $\pm$ 1.6	NR
		Behaviour only	22 (NR/NR)					NR
Martin (1997); <sup>148</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age >18 years) with history of alcohol abuse and dependence with $\geq$ 3 consecutive months of alcohol and drug abstinence; smoked $\geq$ 10 cigarettes/day; physician's approval for the use of nicotine gum and exercise  <i>Exclusion:</i> Use of psychotropic medication; physical disabilities	Nicotine gum + behaviour	63 (33/30)	43.6 $\pm$ 11.0	26.1 $\pm$ 11.7	$\geq$ 10	NR	5.6 $\pm$ 17.6
		Behaviour	70 (38/32)	41.5 $\pm$ 9.7	23.5 $\pm$ 10.0			4.1 $\pm$ 34.0
		Behaviour + exercise	72 (41/31)	40.5 $\pm$ 8.9	23.7 $\pm$ 8.8			2.9 $\pm$ 2.6
Molyneux (2003); <sup>142</sup> RCT, parallel	<i>Inclusion:</i> Medical/surgery inpatients; smokers (age $\geq$ 18 years)  <i>Exclusion:</i> Pregnancy or lactation; psychiatric patient; substance abuse; terminal illness; hypersensitivity to nicotine or menthol	NRT + counselling	91 (58/33)	49.3 $\pm$ 15.9	33.1 $\pm$ 16.6	Median: 20 (range 3-80)	5 (range 3-6)	NR
		Counselling	91 (51/40)	47.8 $\pm$ 15.3	32.1 $\pm$ 15.8	Median: 20 (range: 3-40)	4 (range 2-6)	NR
Niaura (1994); <sup>149</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers recruited from outpatient settings  <i>Exclusion:</i> Pregnancy or lactation; heart disease; hypertension, active peptic ulcer disease; substance abuse; dementia;	Nicotine gum + counselling (Low dependence)	37 (17/20)	44 $\pm$ 13	24.3 $\pm$ 12.8	28.3 $\pm$ 14.0	NR	NR
		Nicotine gum + counselling	47 (27/20)	39 $\pm$ 9	20.9 $\pm$ 8.1			NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
	dentures and periodontal disease; temporomandibular joint disorder	(High dependence)						
		Counselling (Low dependence)	40 (13/27)	44 ± 12	24.3 ± 12.1	23.9 ± 12.2	NR	NR
		Counselling (High dependence)	49 (29/20)	43 ± 9	25.3 ± 9.2	33.4 ± 9.3	NR	NR
Niaura (1999); <sup>150</sup> RCT, parallel	<i>Inclusion:</i> NR <i>Exclusion:</i> Chronic medical condition; major illness, psychiatric disorder; substance abuse; use of other forms of tobacco products	Behaviour + cue exposure + gum	31 (50% female overall)	43.5 ± 11.1	26.9 ± 10.4	27.8 ± 12.0	NR	NR
		Behaviour + cue exposure	31				NR	NR
		Behaviour + gum	35				NR	NR
		Brief behaviour	32				NR	NR
Okuyemi (2007); <sup>151</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age ≥18 years); smoked ≥5 cigarettes/day; current resident of the targeted housing development; no plan to move in the next 6 months; speak English; have a telephone <i>Exclusion:</i> Heart disease; allergy/sensitivity to nicotine gum; jaw problem; hypertension; diabetes	Nicotine gum + counselling	66 (13/53)	43 ± 14.3	NR	19 ± 13.0	NR	NR
		Counselling	107 (39/68)	48 ± 13.1	NR	16 ± 9.2	NR	NR
Pirie (1992); <sup>152</sup> RCT, parallel	<i>Inclusion:</i> Women smokers (20-64 years); motivated-to-quit; concern about weight gain <i>Exclusion:</i> Medical reasons that contraindicate use of nicotine gum; pregnancy or lactation; gastric ulcer; substance abuse; hypertension; temporomandibular joint syndrome; cancer	FFS	103 (0/103)	42.3	NR	25.6	NR	NR
		Gum + FFS	108 (0/108)	42.9	NR	27.1	NR	NR
		Behaviour + FFS	108 (0/108)	44.0	NR	26.9	NR	NR
		Gum + FFS + behaviour	98 (0/98)	43.4	NR	25.1	NR	NR
Pollak (2007); <sup>153</sup>	<i>Inclusion:</i> Women smokers (≥18 years); 13-25 wks pregnant; smoked ≥5	NRT + behaviour	122 (0/122)	27 ± 6	NR	11 ± 5	3 ± 1	6 ± 1

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
RCT, parallel	cigarettes/day <i>Exclusion:</i> Evidence of cognitive or mental health problem; substance abuse; history of placental abruption; uncontrolled hypertension; heart disease; previous pregnancy with congenital anomaly	Behaviour	59 (0/59)	26 ± 5	NR	12 ± 5	3 ± 1	6 ± 1
Richmond (1993); <sup>156</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age 16-65 years), speak English <i>Exclusion:</i> Pregnancy; cardiovascular disease; angina; gastric; peptic ulcer; any medical condition that contraindicates the use of nicotine gum	Nicotine gum + behaviour	200 (NR/NR); 60% female overall	35	17	22	NR	NR
		Behaviour	150 (NR/NR)				NR	NR
		Gum + GP advice	100 (NR/NR)				NR	NR
Segnan (1991); <sup>157</sup> RCT, parallel	<i>Inclusion:</i> Recruited smokers (age 20-60 years); free of life threatening disease <i>Exclusion:</i> NR	Nicotine gum + counselling	294 (186/108)	20-60	NR	NR	NR	NR
		Counselling	275 (166/109)		NR	NR	NR	NR
<b>NRT doses</b>								
Jorenby (1995); <sup>384</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers (age ≥20 years); smoked ≥15 cigarettes/day for ≥1 year; the only member of the household participating in the study <i>Exclusion:</i> Allergy or hypersensitivity to transdermal adhesives; use of other nicotine-containing products; use of other form of tobacco products; heart disease; cerebrovascular, pregnancy or lactation	22-mg patch + minimal counselling	85 (38/47)	44.6 ± 11.7	NR	26.1 ± 8.9	7.3 ± 1.7	3.8 (4.1)
		22-mg patch + individual counselling	80 (45/35)	45.1 ± 11	NR	26.3 ± 8.4	7.1 ± 1.8	2.8 (2.1)
		22-mg patch + group counselling	87 (39/48)	44.2 ± 12.4	NR	27.8 ± 10.2	7.4 ± 1.7	2.6 (2.0)
		44-mg patch + minimal counselling	84 (38/46)	45.5 ± 12.2	NR	29.3 ± 12.7	7.1 ± 2.1	3.1 (3.5)
		44-mg patch + individual	88 (37/51)	43.1 ± 11.6	NR	27.7 ± 10.2	7.4 ± 2.0	3.0 (2.5)

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
		counselling						
		44-mg patch + group counselling	80 (38/42)	43.0 ± 10.9	NR	28.1 ± 10.3	7.4 ± 1.8	2.8 (1.9)
Killen (1999); <sup>385</sup> RCT, parallel	<i>Inclusion:</i> Recruited heavy smokers (age >18 yrs); smoked >25 cigarettes/day;  <i>Exclusion:</i> Pregnancy; lactation; depression; schizophrenia; peptic ulcer. Those with history of heart disease, chest pain, diabetes, thyroid disease required permission from their physician	15-mg patch	202 (117/85)	46.6 ± 10.5	NR	36.6 ± 10.8	18.9 ± 3.1 (modified)	NR
		25-mg patch	206 (122/84)	47.9 ± 10.6	NR	35.2 ± 9.4	18.4 ± 3.4 (modified)	NR
<b>Bupropion vs. placebo</b>								
Ahluwalia (2002); <sup>158</sup> RCT, double-blind, parallel	<i>Inclusion:</i> African American or black smokers (age ≥18 years); smoked ≥10 cigarettes/day; motivated-to-quit  <i>Exclusion:</i> Contraindication for bupropion (seizure; alcohol abuse; bulimia or anorexia nervosa; pregnancy; use of psychoactive medication; use of other forms of tobacco or NRT in the past 30 days); current treatment for depression	Bupropion (150 mg, BID)	300 (88/212)	44 ± 10.9	NR	16.1 ± 7.5	4.6 ± 2.1	2.1 ± 4.7
		Placebo	300 (92/208)	44.4 ± 11.3	NR	17.1 ± 8.5	4.7 ± 1.9	2.2 ± 4.2
Aubin (2004); <sup>173</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥18 years); smoked ≥10 cigarettes/day; general good health  <i>Exclusion:</i> Epilepsy or seizures; anorexia nervosa or bulimia; bipolar; panic disorder or psychosis; history of alcohol abuse; severe hepatic, renal or neurological disease; cardiovascular disease; hypertension; pregnancy or lactation	Bupropion (150 mg, BID)	340 (150/190)	41 ± 10	NR	NR	5.8 ± 2.1	2 (range 0-25)
		Placebo	164 (74/90)	41 ± 10	NR	NR	5.4 ± 2.3	2 (range 0-30)
Brown (2007); <sup>159</sup> RCT, double-	<i>Inclusion:</i> Motivated-to-quit smokers; smoked ≥10 cigarettes/day over the past year	Bupropion (150 mg, BID)	255 (130/125)	43.6 ± 10.3	26	24.3 ± 9.6	6.41 (1.9)	NR
		Placebo	269	44.8 ± 10.4		25.5 ± 10.5		NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
blind, parallel	<i>Exclusion:</i> Mental disorders; use of psychoactive drugs or psychotropic medication; use of other forms of tobacco products; hypertension; pregnancy or lactation; refusal to use contraception; seizure; head injury; eating disorder; panic disorder		(145/124)					
Evins (2001, 2004); <sup>160,181</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Schizophrenia outpatients at a mental health centre; on stable dose of antipsychotic medications for at least 4 wks, smoked $\geq$ 1/2 pack/day; desire to quit smoking  <i>Exclusion:</i> Acute exacerbation of psychosis; substance abuse; bulimia; seizure; major depression	Bupropion (150 mg/day)	9 (6/3)	45.5 $\pm$ 7.2	NR	38 $\pm$ 20	NR	NR
		Placebo	9 (5/4)	42.7 $\pm$ 7.9	NR	30 $\pm$ 20	NR	NR
Evins (2005); <sup>161</sup> RCT, parallel	<i>Inclusion:</i> Schizophrenia outpatients at a mental health centre; on stable dose of antipsychotic medications for at least 4 wks, smoked $\geq$ 10 cigarettes/day; desire to quit smoking  <i>Exclusion:</i> Acute exacerbation of psychosis; substance abuse; bulimia; seizure; major depression	Bupropion (150 mg, BID)	25 (19/6)	46.0 $\pm$ 9.4	NR	34.2 $\pm$ 20.4	NR	2 (range 0-50)
		Placebo	28 (20/8)	45.5 $\pm$ 8.3	NR	25.4 $\pm$ 12.2	NR	
Fossati (2007); <sup>174</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Smokers (age $\geq$ 18 years) recruited by GPs; smoked $\geq$ 10 cigarettes/day for the previous year; motivated-to-quit; good health; bupropion naïve  <i>Exclusion:</i> History of seizure; eating disorders; severe renal, hepatic, neurological, or chronic pulmonary disease	Bupropion (150 mg, BID)	400 (248/152)	Median: 49.4	NR	21.1 $\pm$ 8.7	5.0 $\pm$ 2.1	NR
		Placebo	193 (107/86)	Median: 48.5	NR	21.6 $\pm$ 9.4	5.2 $\pm$ 2.0	NR
George (2002); <sup>162</sup>	<i>Inclusion:</i> Schizophrenic smokers; motivated-to-quit; clinically stable for	Bupropion (150 mg, BID)	16 (10/6)	45.4 $\pm$ 11.9	NR	25.0 $\pm$ 11.5	7.1 $\pm$ 0.9	2.9 $\pm$ 2.9

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
RCT, double-blind, parallel	psychotic and affective symptomatology <i>Exclusion:</i> History of substance abuse or dependence; epilepsy or seizure history	Placebo	16 (8/8)	40.9 ± 9.4	NR	23.3 ± 9.5	7.3 ± 1.6	4.3 ± 5.3
Gonzales (2001); <sup>163</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers age (≥18 years); smoked ≥15 cigarettes/day; CO levels >10 ppm; use of bupropion as an aid for smoking cessation for at least 2 wks; one participant per household <i>Exclusion:</i> Seizure, bulimia, or anorexia nervosa; severe renal, hepatic or chronic pulmonary disease; major depression; currently using another treatment for smoking cessation	Bupropion (150 mg, BID)	226 (118/108)	44.5 ± 11.8	NR	≥15	7.0 ± 1.7	4.8 ± 4.6
		Placebo	224 (101/123)	45.5 ± 11.2	NR		7.2 ± 1.7	4.6 ± 7.3
Haggström (2006); <sup>175</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥18 years); smoked ≥10 pack years; FTND score ≥4 <i>Exclusion:</i> Serious or unstable clinical or psychiatric disorder; severe depression; pregnancy or lactation; substance abuse; currently under smoking cessation treatments; use of other forms of tobacco; history of seizures; myocardial infarction; use of monoaminooxidase inhibitors	Bupropion (150 mg, BID)	53 (22/31)	45.5 ± 10.7	NR	NR	6.2 ± 1.8	NR
		Placebo	51 (15/36)	41.5 ± 10.4	NR	NR	5.9 ± 1.8	NR
Hall (2002); <sup>164</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers; smoked ≥10 cigarettes/day <i>Exclusion:</i> Cardiovascular disease; hyperthyroidism; seizure or bulimia; use of monoaminooxidase inhibitors within 2 wks; severe allergies; life-threatening disease; bipolar disease; major depression; pregnancy or lactation; migraine; previous use of bupropion for smoking cessation; substance abuse; psychiatric disorders; current NRT use	Bupropion (150 mg, BID) + MM	36 (21/15)	37.1 ± 9.7	19.7 ± 10.2	19.8 ± 7.5	4.1 ± 2.2	6.3 ± 8.0
		Placebo + MM	37 (22/15)	43.4 ± 11.8	24.7 ± 11.8	23.0 ± 10.6	5.4 ± 2.3	7.0 ± 11.9
		Bupropion (150 mg, BID) + PI	37 (20/17)	37.9 ± 11.4	21.2 ± 11.6	22.5 ± 9.0	5.1 ± 2.3	4.6 ± 4.1
		Placebo + PI	36 (19/17)	39.3 ± 10.2	21.2 ± 9.9	22.2 ± 9.5	4.7 ± 2.0	6.8 ± 9.9

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Hatsukami (2004); <sup>165</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-reduce smokers (age $\geq$ 18 years); smoked $\geq$ 20 cigarettes/day; unwilling or unable to quit  <i>Exclusion:</i> Under current smoking reduction or cessation treatment; use of other forms of tobacco; seizure; eating disorder; heart disease; use of drugs that interfere with bupropion; psychiatric illness; substance abuse	Bupropion (150 mg, BID)	295 (169/126)	42.5 $\pm$ 11.0	NR	29.0 $\pm$ 9.8	6.4 $\pm$ 1.8	4.2 $\pm$ 3.6
		Placebo	299 (158/141)	42.0 $\pm$ 11.6	NR	28.5 $\pm$ 9.6	6.4 $\pm$ 1.8	5.0 $\pm$ 4.6
Hertzberg (2001); <sup>166</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Vietnam combat veterans; smokers with posttraumatic stress disorder; either receiving no psychotropic medication or a stable psychotropic regimen  <i>Exclusion:</i> NR	Bupropion (150 mg, BID)	10 (10/0)	50 (range: 47-58)	NR	33 (range: 15-99)	NR	NR
		Placebo	5 (5/0)		NR		NR	NR
Holt (2005); <sup>176</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Maori smokers (age 16-70 years); smoked $\geq$ 10 cigarettes/day; desire to stop smoking  <i>Exclusion:</i> History of epilepsy; febrile convulsions; CNS tumour; head injury; cerebrovascular disease; anorexia or bulimia; cardiovascular disease; uncontrolled hypertension; severe renal, hepatic or neurological disease; history of substance abuse; unwillingness to stop smoking marijuana; positive pregnancy test	Bupropion (150 mg, BID)	88 (27/61)	41.7 $\pm$ 9.2	NR	NR	5.8 $\pm$ 2.2	NR
		Placebo	46 (11/35)	38.0 $\pm$ 11.1	NR	NR	5.3 $\pm$ 2.0	NR
Hurt (1997); <sup>167</sup> RCT, double-blind, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 18 years); smoked $\geq$ 15 cigarettes/day for the past year; generally good health  <i>Exclusion:</i> Seizure; severe head trauma; predisposition to seizures; anorexia nervosa or bulimia; psychiatric condition; pregnancy or lactation; substance abuse;	Bupropion (150 mg, BID)	156 (77/79)	45.0 $\pm$ 11.8	NR	27.2 $\pm$ 10.8	7.1 $\pm$ 1.7	4.3 $\pm$ 5.4
		Bupropion (150 mg/day)	153 (76/77)	42.3 $\pm$ 11.3	NR	27.5 $\pm$ 9.6	7.3 $\pm$ 1.6	4.2 $\pm$ 6.5
		Bupropion (50 mg, BID)	153 (64/89)	44.1 $\pm$ 10.5	NR	26.2 $\pm$ 8.5	7.3 $\pm$ 1.6	3.5 $\pm$ 3.4
		Placebo	153	43.0 $\pm$ 10.7	NR	26.5 $\pm$ 9.0	7.3 $\pm$ 1.7	3.7 $\pm$ 5.0

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	current use of psychiatric medications; previous use of bupropion; current use of medication for smoking cessation; depression		(62/91)					
McCarthy (2008); <sup>168</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq 18$ years); smoked $\geq 10$ cigarettes/day; expired CO $>9$ ppm  <i>Exclusion:</i> Serious psychopathology (bipolar disorder, or psychosis); current depression; contraindications to use of bupropion (uncontrolled hypertension, history of seizure, history of eating disorder, heavy drinking, pregnancy or lactation)	Bupropion (150 mg, BID, $\pm$ counselling)	229 (120/109)	38.9 $\pm$ 12.0	NR	22.2 $\pm$ 10.7	5.1 $\pm$ 2.4	5.0 $\pm$ 7.1
		Placebo ( $\pm$ counselling)	234 (110/124)	38.6 $\pm$ 12.1	NR	21.7 $\pm$ 10.0	5.1 $\pm$ 2.3	6.9 $\pm$ 12.6
Muramoto (2007); <sup>169</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit adolescent smokers (age 14-17 years); smoked $\geq 6$ cigarettes/day; CO levels $\geq 10$ ppm; $\geq 2$ previous quit attempts, weight $\geq 40.5$ kg  <i>Exclusion:</i> Current use of other forms of tobacco products or smoking cessation treatments; panic disorder; psychosis; eating disorder; substance abuse or dependence; depression, ADHD; psychoactive drug treatment; seizure; cardiovascular disease; pregnancy or lactation or girls unwilling to use contraception	Bupropion (150 mg, BID)	104 (60/44)	Median: 16	Median: 4	Median: 12	NR	$\geq 2$
		Bupropion (150 mg/day)	105 (49/56)	Median: 16	Median: 4	Median: 10	NR	$\geq 2$
		Placebo	103 (60/43)	Median: 16	Median: 4	Median: 11	NR	$\geq 2$
Simon (2009); <sup>172</sup> RCT, double-blind parallel	<i>Inclusion:</i> Adult patients who smoked and were admitted to the hospital for $\geq 24$ h; smoked $\geq 5$ cigarettes/day during the previous year  <i>Exclusion:</i> Contraindications to bupropion; myocardial infarction or unstable angina;	Bupropion (150 mg, BID, + counselling)	42 (39/3)	55 $\pm$ 8	NR	16 $\pm$ 11	4.4 $\pm$ 2.1	NR
		Placebo (+ counselling)	43 (43/0)	57 $\pm$ 7	NR	16 $\pm$ 9	4.4 $\pm$ 2.2	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	terminal illness; serious unstable psychiatric illness; seizures; head trauma; pregnancy or lactation; substance abuse							
Rigotti (2006); <sup>170</sup> RCT, double-blind parallel	<i>Inclusion:</i> Patients (age >18 years) admitted with acute cardiovascular disease; smoked >1 cigarettes/day in the past month; motivated-to-quit  <i>Exclusion:</i> Risk of seizure; high blood pressure; heavy alcohol use; severe hepatic or renal disease; major depression; psychosis; cognitive impairment; life expectancy <12 months; recent use of illegal drug	Bupropion (150 mg, BID)	124 (86/38)	56.7 $\pm$ 9.7	38.8 $\pm$ 10.1	23.1 $\pm$ 13.9	5.3 $\pm$ 2.4	NR
		Placebo	124 (86/38)	54.9 $\pm$ 9.7	36.5 $\pm$ 11.9	20.5 $\pm$ 10.5	5.0 $\pm$ 2.2	NR
Tashkin (2001); <sup>171</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 35 years) with stage I or II COPD; smoked $\geq$ 15 cigarettes/day for the previous year; did not stop smoking for more than 3 months during that year  <i>Exclusion:</i> Serious or unstable medical disorders affecting lung function; bupropion contraindications; major depression; use of oral corticosteroids or theophylline	Bupropion (150 mg, BID)	206 (113/93)	53.2 $\pm$ 9.0	NR	28.7 $\pm$ 11.1	7.1 $\pm$ 1.7	NR
		Placebo	205 (113/92)	54.5 $\pm$ 9.5	NR	27.6 $\pm$ 10.2	7.0 $\pm$ 1.7	NR
Tønnesen (2003); <sup>178</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 18 years); smoked $\geq$ 10 cigarettes/day for the previous year; did not stop smoking for more than 3 months during that year  <i>Exclusion:</i> Serious medical conditions	Bupropion (150 mg, BID)	527 (253/274)	42.4 $\pm$ 9.8	NR	22.4 $\pm$ 8.2	5.5 $\pm$ 1.9	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	(cardiac, gastrointestinal, hepatic, renal, hematological, neurological, and psychiatric disease); seizure; major depression; bulimia; anorexia nervosa; panic disorder; psychosis or bipolar disorder; uncontrolled hypertension; use of NRT during previous 3 months; previous use of bupropion for smoking cessation; use of other smoking cessation treatments	Placebo	180 (90/90)	41.9 $\pm$ 9.5	NR	23.5 $\pm$ 9.8	5.4 $\pm$ 2.0	NR
Tonstad (2003); <sup>179</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers; smoked $\geq$ 10 cigarettes/day for the previous year; did not stop smoking during the previous 3 months; had at least one cardiovascular condition (i.e., myocardial infarction, interventional cardiac procedure, stable angina pectoris, peripheral vascular disease, congestive heart failure); controlled hypertension  <i>Exclusion:</i> Chronic medical conditions; hepatic, renal, hematological, neurological, or pulmonary disease; seizure; major depression; bulimia; anorexia nervosa; panic disorder; psychosis or bipolar disorder	Bupropion (150 mg, BID)	313 (232/81)	55.6 $\pm$ 9.2	NR	25.2 $\pm$ 12.2	6.5 $\pm$ 2.0	6.1 $\pm$ 12.3
		Placebo	313 (247/66)	55.1 $\pm$ 9.0	NR	25.6 $\pm$ 11.7	6.6 $\pm$ 2.0	4.7 $\pm$ 8.2
Wagena (2005); <sup>177</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 30-70 years) at risk for COPD or with COPD; smoked $\geq$ 10 cigarettes/day during the last year for $\geq$ 5 years  <i>Exclusion:</i> Use of bupropion, NRT or psychoactive medication at the time of assessment; serious or unstable medical disorders that might affect lung function	Bupropion (150 mg, BID)	86 (34/52)	51.1 $\pm$ 8.3	NR	24.2 $\pm$ 9.4	6.2 $\pm$ 2.1	NR
		Placebo	89 (46/43)	51.3 $\pm$ 8.4	NR	23.6 $\pm$ 8.8	5.9 $\pm$ 2.1	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
Zellweger (2005); <sup>180</sup> RCT, double-blind parallel	<i>Inclusion:</i> Health care professional smokers (physician or nurse, age $\geq$ 18 years); motivated-to-quit; smoked $\geq$ 10 cigarettes/day during the last year; no serious attempt to quit during the previous 12 months <i>Exclusion:</i> Seizures; hepatic, renal, hematological, neurological, or pulmonary disease; seizure; major depression; bulimia; anorexia nervosa; panic disorder; psychosis or bipolar disorder; uncontrolled hypertension; use of NRT during the previous 6 months; previous use of bupropion for smoking cessation; use of other smoking cessation treatments; pregnancy or lactation	Bupropion (150 mg, BID)	501 (180/321)	40.3 $\pm$ 8.9	NR	22.3 $\pm$ 8.0	6.1 $\pm$ 1.9	NR
		Placebo	166 (60/106)	40.3 $\pm$ 9.1	NR	23.8 $\pm$ 9.0	6.2 $\pm$ 2.0	NR
<b>Bupropion vs. nicotine patch</b>								
Uyar (2007); <sup>182</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 18-75 years); smoked $\geq$ 10 cigarettes/day for $\geq$ 1 year <i>Exclusion:</i> Depression; pregnancy or lactation; symptomatic cardiac disease; regular psychotropic drug use; substance abuse; skin allergy to nicotine patch; head trauma or convulsion	Nicotine patch	50 (40/10)	36.3 $\pm$ 12.7	NR	$\geq$ 10	4.5	NR
		Bupropion (150 mg, BID)	50 (44/6)	36.0 $\pm$ 10.5	NR	$\geq$ 10	4.8	NR
<b>Bupropion vs. bupropion + counselling</b>								
McCarthy (2008); <sup>168</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq$ 18 years) <i>Exclusion:</i> Serious psychopathology (bipolar disorder, or psychosis); current depression; contraindications to use of bupropion (uncontrolled hypertension, history of seizure, history of eating disorder, heavy drinking, pregnancy or lactation)	Bupropion (150 mg, BID)	116 (59/57)	41.0 $\pm$ 12.6	NR	22.5 $\pm$ 10.1	5.1 $\pm$ 2.3	5.9 $\pm$ 9.8
		Bupropion (150 mg, BID) + counselling	113 (61/52)	36.8 $\pm$ 11.4	NR	21.9 $\pm$ 11.2	5.1 $\pm$ 2.5	4.1 $\pm$ 4.4

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
<b>Nicotine patch + nicotine nasal spray vs. nicotine patch + placebo spray</b>								
Blondal (1999); <sup>183</sup> RCT, double-blind parallel	<i>Inclusion:</i> Smokers (age 21-69 years); smoked ≥1 cigarettes/day for ≥3 years  <i>Exclusion:</i> Myocardial infarction; severe nasal allergy or skin disease; use of smokeless tobacco; misuse of alcohol; pregnancy or lactation	Patch + spray	118 (43/75)	41 (range: 23-62)	NR	25.6 ± 15.7	5.7	NR
		Patch + placebo spray	119 (35/84)	43 (range: 22-66)	NR	25.0 ± 10.9	5.7	NR
<b>Nicotine inhaler + nicotine patch vs. nicotine inhaler + placebo patch</b>								
Bohadana (2000, 2003); <sup>184,364</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age 18-70 years); smoked ≥10 cigarettes/day for ≥3 years; expired CO levels ≥10 ppm  <i>Exclusion:</i> Heart disease; renal, pulmonary, endocrine or neurological disorders; pregnancy or lactation; use of any form of smokeless tobacco or nicotine substitution; substance abuse; use of psychoactive drugs; skin disease	Inhaler + patch	200 (99/101)	37.1 ± 8.1	20.7 ± 8.0	26.1 ± 11.0	6.3 ± 1.9	2.8 ± 2.2
		Inhaler + placebo patch	200 (97/103)	37.4 ± 8.8	20.4 ± 7.8	23.5 ± 8.6	6.1 ± 2.0	3.1 ± 2.8
Piper (2007); <sup>187</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers; smoked ≥10 cigarettes/day  <i>Exclusion:</i> Pregnancy or lactation; any physical or mental health issues	Bupropion (105 mg, BID + gum (4 mg)	228 (101/127)	41.1 ± 11.3	NR	22.1 ± 8.9	5.7 ± 2.2	6.0 ± 13.6
		Bupropion + placebo gum	224 (89/135)	42.3 ± 11.4	NR	23.4 ± 10.8	5.7 ± 2.0	5.6 ± 10.6
		Placebo	156 (66/90)	42.0 ± 11.3	NR	21.6 ± 9.8	5.5 ± 2.2	6.7 ± 16.0
<b>NRT + bupropion vs. NRT + placebo bupropion</b>								
Evins (2007); <sup>191</sup> RCT, double-blind parallel	<i>Inclusion:</i> Adult smokers with schizophrenia; smoked ≥10 cigarettes/day for the past year; motivated-to-quit  <i>Exclusion:</i> Major depression; taking bupropion or NRT during the month before study; seizure or bulimia; on clozapine (>500 mg/day)	NRT + bupropion (105 mg, BID)	25 (NR/NR)	44.8 ± 9.2	NR	28.1 ± 14.3	7.2 ± 1.9	NR
		NRT + placebo	26 (NR/NR)	43.6 ± 10.9	NR	24.7 ± 10.1	7.1 ± 1.7	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
George (2008); <sup>190</sup> RCT, double-blind parallel	<i>Inclusion:</i> Adult smokers with schizophrenia; smoked ≥10 cigarettes/day; motivated-to-quit; expired CO level >10 ppm; on stable dose of antipsychotic drugs for ≥1 month  <i>Exclusion:</i> Substance abuse; seizure; psychiatric instability; unstable medical condition	Nicotine patch + bupropion (105 mg, BID)	29 (17/12)	41.2 ± 9.2	22.9 ± 10.1	24.3 ± 10.3	6.8 ± 1.8	NR
		Nicotine patch + placebo	29 (18/11)	39.3 ± 6.9	22.2 ± 8.9	22.4 ± 11.9	6.8 ± 1.7	NR
Killen (2004); <sup>192</sup> RCT, double-blind parallel	<i>Inclusion:</i> Adolescent smokers (age 15-18 years); smoked ≥10 cigarettes/day for ≥ 6 months; one or more failed attempts to quit smoking; scored ≥10 on modified Fagerström Tolerance Questionnaire  <i>Exclusion:</i> NR	Nicotine patch + bupropion (105 mg/day)	103 (71/32)	17.3 ± 0.7	NR	15.1 ± 5.3	NR	NR
		Nicotine patch + placebo	108 (75/33)	17.3 ± 0.8	Nr	15.7 ± 6.4	NR	NR
Simon (2004); <sup>193</sup> RCT, double-blind parallel	<i>Inclusion:</i> Recruited smokers (age ≥20 years); smoked ≥20 cigarettes/day during the week before enrollment  <i>Exclusion:</i> Contraindications to bupropion or NRT; serious psychiatric illnesses; major depression; alcohol abuse	Nicotine patch + bupropion (105 mg, BID)	121 (106/15)	50 ± 12	NR	22 ± 15	3.8 ± 1.7	NR
		Nicotine patch + placebo	123 (103/20)	49 ± 11	NR	23 ± 11	4.0 ± 1.7	NR
<b>Bupropion + nicotine patch vs. bupropion + placebo vs. nicotine patch + placebo vs. placebo</b>								
Jorenby (1999); <sup>188</sup> Smith (2003); <sup>197</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age ≥18 years); smoked ≥15 cigarettes/day; weighed ≥45.4 kg (100 lb); one smoker per household in study  <i>Exclusion:</i> Serious or unstable cardiac, renal, hypertensive, pulmonary, endocrine, or neurologic disorder; ulcers; seizure; skin disorders; use of NRT within past 6 months; pregnancy or lactation; substance abuse; current use of psychoactive drug or other smoking cessation treatment;	Bupropion + nicotine patch	245 (124/121)	43.9 ± 11.6	26.7 ± 11.6	26.8 ± 9.4	7.3 ± 1.8	2.5 ± 2.4
		Bupropion + placebo patch	244 (118/126)	42.3 ± 10.2	24.6 ± 10.5	25.5 ± 8.8	7.4 ± 1.6	3.1 ± 4.7
		Nicotine patch + placebo bupropion	244 (118/126)	44.0 ± 10.9	26.8 ± 11.1	26.5 ± 9.4	7.4 ± 1.7	2.7 ± 2.4
		Two placebos	160 (66/94)	42.7 ± 10.2	25.6 ± 9.9	28.1 ± 10.6	7.5 ± 1.8	2.8 ± 3.0

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years $\pm$ SD)	No. of years smoked (mean $\pm$ SD)	No. of cigarettes/d in past 30 d (mean $\pm$ SD)	FTND scores (mean $\pm$ SD)	No. of previous quit attempts
	previous use of bupropion; use of other forms of tobacco products							
<b>Nicotine patch + nicotine gum vs. nicotine patch + placebo gum vs. placebo</b>								
Kornitzer (1995); <sup>185</sup> RCT, double-blind parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age $\geq 20$ years); smoked $\geq 10$ cigarettes/day during the last year for $\geq 3$ years; willingness to be monitored for 12 months  <i>Exclusion:</i> Cardiovascular disease; pregnancy or lactation; use of psychotropic medication; substance abuse; skin disease; peptic ulcer; use of smokeless tobacco; in any form of smoking cessation program	Nicotine patch + nicotine gum	149 (88/61)	38.0 $\pm$ 10.4	21.6 $\pm$ 8.1	23.9 $\pm$ 8.5	5.9 $\pm$ 2.0	2.0 $\pm$ 2.0
		Nicotine patch + placebo gum	150 (93/57)	38.8 $\pm$ 10.1	22.1 $\pm$ 7.0	26.3 $\pm$ 10.2	6.0 $\pm$ 1.8	2.8 $\pm$ 8.4
Cooney (2009); <sup>186</sup> RCT, double-blind parallel	<i>Inclusion:</i> Volunteer smokers (age $> 18$ years) with substance abuse or dependence; smoked $\geq 15$ cigarettes/day for $\geq 3$ years; motivated-to-stop drinking and smoking; attend a session out-patient treatment program  <i>Exclusion:</i> Allergy or hypersensitivity to nicotine; skin disorder; weight $< 100$ lb; peptic ulcer; hypertension; diabetes; temporomandibular joint disease; cardiovascular disease; pregnancy or lactation or not practicing contraception; use of medication to influence alcohol or tobacco use; homeless or unstable residence; drug abuse	Nicotine patch + nicotine gum	45 (32/13)	45.1 $\pm$ 10.2	$\geq 3$	26.0 $\pm$ 9.16	6.5 $\pm$ 2.3	NR
		Nicotine patch + placebo gum	51 (36/15)	44.8 $\pm$ 10.1		25.0 $\pm$ 10.3	5.5 $\pm$ 2.2	NR
<b>Nicotine patch + nicotine inhaler + bupropion vs. nicotine patch</b>								
Steinberg (2009); <sup>189</sup> RCT, parallel	<i>Inclusion:</i> Physically ill smokers (cardiovascular, vascular, or pulmonary diseases, cancer, hypertension, diabetes, hyperlipidemia, pulmonary infections); age $\geq 18$ years; smoked $\geq 10$ cigarettes/day; CO	Nicotine patch + inhaler + bupropion	63 (23/40)	NR	NR	$\geq 10$	5.2 $\pm$ 1.9	NR

First author, Year; Design	Inclusion/exclusion criteria	Comparison arms	No. of patients (male/female)	Mean age (years ± SD)	No. of years smoked (mean ± SD)	No. of cigarettes/d in past 30 d (mean ± SD)	FTND scores (mean ± SD)	No. of previous quit attempts
	levels >10 ppm <i>Exclusion:</i> Unstable angina; myocardial infarction; arrhythmia; seizure; serious mental illness; use other tobacco products, use bupropion, clonidine, nortriptyline or NRT; pregnancy or lactation; substance abuse	Nicotine patch	64 (22/42)	NR	NR		5.2 ± 2.3	NR
<b>No pay vs. pay</b>								
Hays (1999); <sup>62</sup> RCT, parallel	<i>Inclusion:</i> Motivated-to-quit smokers (age >18 years); smoked ≥15 cigarettes per day during the previous 6 months <i>Exclusion:</i> Pregnancy or lactation; use of any tobacco products other than cigarettes; use of other forms of nicotine	No pay (nicotine patch)	321 (156/165)	43.5 ± 11.2	25.2 ± 11.4	Range: 16 to >40	6.1 ± 2.0	NR
		Pay (nicotine patch)	315 (155/160)	44.3 ± 10.8	25.8 ± 11.5	Range: 16 to >40	6.2 ± 2.0	NR
Kaper (2005); <sup>195</sup> RCT, parallel	<i>Inclusion:</i> Smokers (age ≥18 years); only one smoker per household included in study <i>Exclusion:</i> NR	No pay (Patient reimbursed)	632 (362/270)	39.5 ± 12.9	NR	13.7 ± 9.6	3.5 ± 2.1	NR
		Pay (No reimbursement)	634 (338/296)	39.9 ± 12.8	NR	13.6 ± 9.0	3.3 ± 2.0	NR
Volpp (2009); <sup>194</sup> RCT, parallel	<i>Inclusion:</i> Employees of a multinational company, at work sites throughout the US (age ≥18 yrs); smoked ≥5 cigarettes/day <i>Exclusion:</i> Use of tobacco products other than cigarettes; plans to leave the firm within 18 months	Incentive	436 (286/150)	45.5	NR	20.1	NR	5.7
		Control	442 (287/155)	44.4	NR	19.7	NR	6.7

ID: twice daily; BMI: body mass index; CVD: cardiovascular; FTND: Fagerström Test for Nicotine Dependence (scores range from 0 to 10); No.: number; NR: not reported; NRT: nicotine replacement therapy; QD: once a day; TDS: Tobacco Dependence Screener (scores range from 0 to 10)

## APPENDIX 7: QUALITY ASSESSMENT OF THE INCLUDED TRIALS

Study	Category				
	A	B	C	D	E
<b>Varenicline vs. placebo</b>					
Nakamura (2007) <sup>47</sup>	X				
Niaura (2008) <sup>48</sup>	X				
Oncken (2006) <sup>49</sup>	X				
Tsai (2007) <sup>50</sup>	X				
Wang (2009) <sup>51</sup>	X				
Williams (2007) <sup>52</sup>	X				
<b>Varenicline vs. bupropion vs. placebo</b>					
Gonzales (2006) <sup>54</sup>	X				
Jorenby (2006) <sup>55</sup>	X				
Nides (2006) <sup>56</sup>	X				
<b>Varenicline vs. nicotine patch</b>					
Aubin (2008) <sup>57</sup>	X				
<b>Nicotine patch vs. placebo</b>					
Campbell (1996) <sup>71</sup>			X		
Davidson (1998) <sup>58</sup>			X		
Daughton (1991) <sup>59</sup>				X	
Daughton (1998) <sup>60</sup>			X		
Fiore (1994) <sup>61</sup>		X			
Glavas (2003) <sup>75</sup>			X		
Hays (1999) <sup>62</sup>			X		
Hughes (2003) <sup>63</sup>			X		
Hurt (1994) <sup>64</sup>	X				
ICR group (1993, 1994, 2003) <sup>72,355,356</sup>		X			
Killen (1997) <sup>65</sup>			X		
Lewis (1998) <sup>66</sup>	X				
Oncken (2007) <sup>67</sup>		X			
Paoletti (1996) <sup>76</sup>		X			
Richmond (1994, 1997, 2007) <sup>77,357-359</sup>	X				
Russell (1993) <sup>73</sup>		X			
Sachs (1993) <sup>68</sup>	X				

Study	Category				
	A	B	C	D	E
Stapleton (1995) <sup>74</sup>		X			
Tonnesen (1991, 1992), <sup>360,361</sup> Mikkelsen (1994) <sup>78</sup>	X				
Tonnesen (1999) <sup>80</sup>	X				
TNS group (1991, 1999) <sup>69,362</sup>		X			
Westman (1993) <sup>70</sup>			X		
Wisborg (2000) <sup>79</sup>			X		
<b>Nicotine gum vs. placebo</b>					
Ahluwalia (2006) <sup>81</sup>	X				
Areechon (1988) <sup>99</sup>			X		
Batra (2005) <sup>100</sup>	X				
Blondal (1989) <sup>101</sup>			X		
Clavel-Chapelon (1997) <sup>102</sup>			X		
Cooper (2005) <sup>82</sup>		X			
Fagerström (1982) <sup>95</sup>				X	
Fortmann (1988) <sup>83</sup>		X			
Garvey (2000) <sup>84</sup>	X				
Hall (1987) <sup>85</sup>				X	
Hall (1996) <sup>86</sup>				X	
Herrera (1995) <sup>103</sup>		X			
Hjalmarson (1984) <sup>96</sup>			X		
Hughes (1989) <sup>87</sup>	X				
Jamrozik (1984) <sup>92</sup>				X	
Jarvis (1982) <sup>93</sup>			X		
Kinnunen (2008) <sup>88</sup>		X			
Malcolm (1983) <sup>94</sup>			X		
Oncken (2008) <sup>89</sup>	X				
Schneider (1983) <sup>90</sup>					X
Shiffman (2009) <sup>91</sup>	X				
Tonnesen (1988) <sup>98</sup>	X				
Wennike (2003) <sup>97</sup>	X				
<b>Nicotine lozenge vs. placebo</b>					
Shiffman (2002) <sup>104</sup>	X				

Study	Category				
	A	B	C	D	E
<b>Nicotine sublingual vs. placebo</b>					
Glover (2002) <sup>105</sup>	X				
Tonnesen (2006) <sup>106</sup>	X				
Wallstrom (2000) <sup>107</sup>	X				
<b>Oral nicotine inhaler vs. placebo</b>					
Bolliger (2000) <sup>108</sup>	X				
Hjalmarson (1997) <sup>109</sup>	X				
Rennard (2006) <sup>110</sup>	X				
Schneider (1996) <sup>111</sup>	X				
Tonnesen (1993) <sup>112</sup>	X				
<b>Nicotine nasal spray vs. placebo</b>					
Blondal (1997) <sup>113</sup>	X				
Hjalmarson (1994) <sup>114</sup>	X				
Schneider (1995) <sup>115</sup>	X				
Sutherland (1992) <sup>116</sup>	X				
<b>Nicotine patch vs. nicotine nasal spray</b>					
Croghan (2003) <sup>117</sup>	X				
Lerman (2004) <sup>118</sup>	X				
<b>Nicotine patch vs. nicotine gum vs. placebo</b>					
Moolchan (2005) <sup>119</sup>			X		
<b>Nicotine lozenge vs. nicotine gum</b>					
Pack (2008) <sup>120</sup>	X				
<b>Nicotine patch vs. oral nicotine inhaler</b>					
Tønnesen (2000) <sup>121</sup>	X				
<b>Nicotine mouth spray vs. nicotine gum vs. oral nicotine inhaler</b>					
Bolliger (2007) <sup>122</sup>			X		
<b>Nicotine patch vs. nicotine patch + behaviour</b>					
Alterman (2001) <sup>123</sup>		X			
Bock (2008) <sup>124</sup>		X			
Lando (1997) <sup>125</sup>		X			
Lifrak (1997) <sup>126</sup>			X		
Simon (2003) <sup>127</sup>	X				
Solomon (2000) <sup>128</sup>	X				

Study	Category				
	A	B	C	D	E
Stein (2006) <sup>129</sup>	X				
Wiggers (2006) <sup>130</sup>	X				
<b>Nicotine gum vs. nicotine gum + behaviour</b>					
Fortmann (1995) <sup>131</sup>		X			
Ginsberg (1992) <sup>132</sup>				X	
Hall (1985) <sup>133</sup>				X	
Hall (1987) <sup>85</sup>				X	
Killen (1984) <sup>134</sup>			X		
<b>NRT + behaviour vs. usual care</b>					
Baker (2006) <sup>135</sup>		X			
Lacasse (2008) <sup>141</sup>		X			
Lewis (1998) <sup>66</sup>	X				
Mohiuddin (2007) <sup>138</sup>	X				
Molyneux (2003) <sup>142</sup>	X				
Nagle (2005) <sup>136</sup>		X			
Reid (2008) <sup>139</sup>	X				
Rodríguez-Artalejo (2003) <sup>143</sup>		X			
Simon (1997) <sup>140</sup>			X		
Wakefield (2004) <sup>137</sup>		X			
<b>NRT + behaviour vs. behaviour</b>					
Cinciripini (1996) <sup>145</sup>			X		
Gilbert (1989) <sup>154</sup>			X		
Hand (2002) <sup>155</sup>		X			
Harackiewicz (1988) <sup>146</sup>			X		
Hill (1993) <sup>147</sup>				X	
Martin (1997) <sup>148</sup>		X			
Molyneux (2003) <sup>142</sup>	X				
Niaura (1994) <sup>149</sup>		X			
Niaura (1999) <sup>150</sup>		X			
Okuyemi (2007) <sup>151</sup>		X			
Pirie (1992) <sup>152</sup>		X			
Pollak (2007) <sup>153</sup>	X				
Richmond (1993) <sup>156</sup>		X			

Study	Category				
	A	B	C	D	E
Segnan (1991) <sup>157</sup>		X			
<b>Bupropion vs. placebo</b>					
Ahluwalia (2002) <sup>158</sup>	X				
Aubin (2004) <sup>173</sup>	X				
Brown (2007) <sup>159</sup>	X				
Evins (2001, 2004) <sup>160,181</sup>			X		
Evins (2005) <sup>161</sup>			X		
Fossati (2007) <sup>174</sup>	X				
George (2002) <sup>162</sup>		X			
Gonzales (2001) <sup>163</sup>	X				
Haggström (2006) <sup>175</sup>	X				
Hall (2002) <sup>164</sup>		X			
Hatsukami (2004) <sup>165</sup>	X				
Hertzberg (2001) <sup>166</sup>			X		
Holt (2005) <sup>176</sup>	X				
Hurt (1997) <sup>167</sup>	X				
McCarthy (2008) <sup>168</sup>	X				
Muramoto (2007) <sup>169</sup>	X				
Rigotti (2006) <sup>170</sup>	X				
Simon (2009) <sup>172</sup>	X				
Tashkin (2001) <sup>171</sup>	X				
Tønnesen (2003) <sup>178</sup>	X				
Tonstad (2003) <sup>179</sup>	X				
Wagena (2005) <sup>177</sup>	X				
Zellweger (2005) <sup>180</sup>	X				
<b>Bupropion vs. nicotine patch</b>					
Uyar (2007) <sup>182</sup>			X		
<b>Bupropion vs. bupropion + counselling</b>					
McCarthy (2008) <sup>168</sup>	X				
<b>Nicotine patch + nicotine nasal spray vs. patch + placebo spray</b>					
Blondal (1999) <sup>183</sup>		X			

Study	Category				
	A	B	C	D	E
<b>Nicotine inhaler + nicotine patch vs. inhaler + placebo patch</b>					
Bohadana (2000, 2003) <sup>184,364</sup>	X				
<b>Bupropion + nicotine gum vs. bupropion + placebo gum vs. two placebos</b>					
Piper (2007) <sup>187</sup>	X				
<b>NRT + bupropion vs. NRT + placebo bupropion</b>					
Evins (2007) <sup>191</sup>		X			
George (2008) <sup>190</sup>			X		
Killen (2004) <sup>192</sup>	X				
Simon (2004) <sup>193</sup>	X				
<b>Bupropion + nicotine patch vs. bupropion + placebo patch vs. patch + placebo bupropion vs. placebo</b>					
Jorenby (1999); <sup>188</sup> Smith (2003) <sup>197</sup>	X				
<b>Nicotine patch + nicotine gum vs. patch + placebo gum vs. placebo</b>					
Kornitzer (1995) <sup>185</sup>	X				
Cooney (2009) <sup>186</sup>	X				
<b>Nicotine patch + nicotine inhaler + bupropion vs. nicotine patch</b>					
Steinberg (2009) <sup>189</sup>	X				
<b>No pay vs. pay</b>					
Hays (1999) <sup>62</sup>			X		
Kaper (2005) <sup>195</sup>	X				
Volpp (2009) <sup>194</sup>	X				

## APPENDIX 8: CLINICAL EFFECTS ON CESSATION RATES AND RELAPSE

Appendix 8a: NRT vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>CAR at 6 m</b>							
NRT vs. placebo (27)		0.783 (0.046)	2.19	1.99-2.40	0.805 (0.061)	2.24	1.98-2.53
Bupropion vs. placebo (10)		0.678 (0.088)	1.97	1.65-2.35	0.699 (0.101)	2.01	1.64-2.46
Varenicline vs. placebo (7)		0.987 (0.078)	2.68	2.29-3.14	0.992 (0.096)	2.70	2.23-3.26
Bupropion vs. NRT(0)		-0.105 (0.099)	0.90	0.74-1.10	-0.107 (0.113)	0.90	0.72-1.13
Varenicline vs. NRT (1)		0.204 (0.091)	1.23	1.02-1.47	0.186 (0.105)	1.20	0.98-1.49
Varenicline vs. Bupropion (3)		0.309 (0.118)	1.36	1.08-1.72	0.293 (0.116)	1.34	1.06-1.69
P(placebo is best)	0.0						
P (NRT is best)	3.2						
P (Bupropion is best)	1.0						
P (Varenicline is best)	95.8						
Placebo rate (SE): 0.115 (0.010)							
<b>CAR at 1 y</b>							
NRT vs. placebo (29)		0.604 (0.052)	1.83	1.65-2.03	0.634 (0.072)	1.89	1.63-2.18
Bupropion vs. placebo (9)		0.637 (0.089)	1.89	1.58-2.26	0.667 (0.106)	1.95	1.58-2.41
Varenicline vs. placebo (6)		0.993 (0.091)	2.70	2.25-3.24	1.023 (0.125)	2.78	2.17-3.57
Bupropion vs. NRT (1)		0.033 (0.103)	1.03	0.84-1.27	0.033 (0.124)	1.03	0.81-1.32
Varenicline vs. NRT (1)		0.389 (0.105)	1.47	1.20-1.82	0.388 (0.134)	1.47	1.13-1.93
Varenicline vs. Bupropion (3)		0.355 (0.127)	1.43	1.11-1.84	0.356 (0.141)	1.43	1.08-1.89
P(placebo is best)	0.0						
P (NRT is best)	0.3						
P (Bupropion is best)	0.5						
P (Varenicline is best)	99.2						
Placebo rate (SE): 0.098 (0.009)							
<b>CAR at 2 y</b>							

**Appendix 8a: NRT vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
NRT vs. placebo (6)		0.960 (0.189)	2.61	1.79-3.81	1.045 (0.327)	2.84	1.48-5.47
P(placebo is best)	0.2						
P (NRT is best)	99.8						
Placebo rate (SE): 0.058 (0.037)							
<b>CAR at 3 y</b>							
NRT vs. placebo (2)		1.191 (0.345)	3.29	1.65-6.56	1.258 (0.706)	3.52	0.86-14.43
P(placebo is best)	3.1						
P (NRT is best)	96.9						
Placebo rate (SE): 0.046 (0.039)							
<b>CAR at 4 y</b>							
NRT vs. placebo (1)		0.002 (0.266)	1.00	0.59-1.71	-0.008 (0.261)	0.99	0.59-1.67
P(placebo is best)	50.9						
P (NRT is best)	49.1						
Placebo rate (SE): none							
<b>CAR at 5 y</b>							
NRT vs. placebo (2)		0.574 (0.302)	1.78	0.97-3.25	0.543 (0.731)	1.72	0.40-7.43
P(placebo is best)	17.1						
P (NRT is best)	82.9						
Placebo rate (SE): 0.099 (0.090)							
<b>CAR at 7 y</b>							
NRT vs. placebo (1)		1.478 (0.571)	4.38	1.40-13.74	1.424 (0.588)	4.15	1.28-13.45
P(placebo is best)	0.5						
P (NRT is best)	99.5						
Placebo rate (SE): none							
<b>CAR at 8 y</b>							
NRT vs. placebo (1)		0.326 (0.228)	1.39	0.88-2.19	0.317 (0.230)	1.37	0.87-2.18
P(placebo is best)	8.7						
P (NRT is best)	91.3						
Placebo rate (SE): none							

**Appendix 8a: NRT vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b><i>CAR at 10 y</i></b>							
NRT vs. placebo (1)		1.161 (0.589)	3.19	0.98-10.37	1.090 (0.577)	2.97	0.94-9.42
P(placebo is best)	2.5						
P (NRT is best)	97.5						
Placebo rate (SE): none							
<b><i>PAR at 6 m</i></b>							
Bupropion vs. placebo (1)		0.580 (0.227)	1.79	1.13-2.81	0.583 (1.125)	1.79	0.19-16.99
NRT vs. placebo (1)		0.794 (0.276)	2.21	1.27-3.84	0.783 (1.154)	2.19	0.22-21.99
NRT vs. bupropion (0)		0.214 (0.357)	1.24	0.61-2.53	0.199 (1.675)	1.22	0.04-34.80
P(placebo is best)	5.0						
P (NRT is best)	40.5						
P (Bupropion is best)	54.5						
Placebo rate (SE): 0.219 (0.105)							
<b><i>PAR at 1 y</i></b>							
NRT vs. placebo (4)		0.880 (0.173)	2.41	1.71-3.41	0.908 (0.295)	2.48	1.37-4.47
Bupropion vs. placebo (1)		0.443 (0.256)	1.56	0.93-2.60	0.477 (0.524)	1.61	0.57-4.59
Varenicline vs. placebo (1)		0.774 (0.234)	2.17	1.36-3.47	0.785 (0.488)	2.19	0.83-5.82
Bupropion vs. NRT (0)		-0.437 (0.309)	0.65	0.35-1.20	-0.431 (0.607)	0.65	0.19-2.19
Varenicline vs. NRT (0)		-0.105 (0.291)	0.90	0.50-1.61	-0.122 (0.573)	0.88	0.28-2.79
Varenicline vs. Bupropion (0)		0.331 (0.347)	1.39	0.70-2.79	0.308 (0.722)	1.36	0.32-5.76
P(placebo is best)	0.0						
P (NRT is best)	52.8						
P (Bupropion is best)	12.5						
P (Varenicline is best)	34.7						
Placebo rate (SE): 0.158 (0.034)							
<b><i>PPA at 6 m</i></b>							
NRT vs. placebo (16)		0.566 (0.068)	1.76	1.54-2.02	0.572 (0.079)	1.77	1.51-2.08
Bupropion vs. placebo (13)		0.634 (0.059)	1.88	1.67-2.12	0.638 (0.073)	1.89	1.64-2.19
Varenicline vs. placebo (4)		0.978 (0.084)	2.66	2.25-3.15	0.993 (0.108)	2.70	2.17-3.35

**Appendix 8a: NRT vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Bupropion vs. NRT (2)		0.068 (0.090)	1.07	0.89-1.28	0.067 (0.100)	1.07	0.88-1.30
Varenicline vs. NRT (1)		0.412 (0.108)	1.51	1.22-1.88	0.422 (0.122)	1.52	1.19-1.95
Varenicline vs. Bupropion (2)		0.344 (0.103)	1.41	1.15-1.73	0.355 (0.114)	1.43	1.14-1.79
P(placebo is best)	0.0						
P (NRT is best)	0.0						
P (Bupropion is best)	0.0						
P (Varenicline is best)	100						
Placebo rate (SE): 0.179 (0.017)							
<b>PPA at 1 y</b>							
NRT vs. placebo (17)		0.623 (0.073)	1.86	1.61-2.16	0.663 (0.102)	1.94	1.58-2.38
Bupropion vs. placebo (10)		0.603 (0.068)	1.83	1.59-2.09	0.618 (0.110)	1.86	1.49-2.31
Varenicline vs. placebo (5)		0.888 (0.082)	2.43	2.06-2.87	0.934 (0.141)	2.55	1.92-3.38
Bupropion vs. NRT (1)		-0.020 (0.100)	0.98	0.80-1.20	-0.045 (0.138)	0.96	0.73-1.26
Varenicline vs. NRT (1)		0.265 (0.110)	1.30	1.05-1.62	0.271 (0.156)	1.31	0.96-1.79
Varenicline vs. Bupropion (2)		0.285 (0.107)	1.33	1.07-1.65	0.316 (0.155)	1.37	1.01-1.87
P(placebo is best)	0.0						
P (NRT is best)	3.4						
P (Bupropion is best)	1.3						
P (Varenicline is best)	95.3						
Placebo rate (SE): 0.135 (0.016)							
<b>PPA at 15 m</b>							
NRT vs. placebo (1)		1.798 (0.634)	6.04	1.70-21.46	1.727 (0.621)	5.62	1.62-19.47
P(placebo is best)	0.1						
P (NRT is best)	99.9						
Placebo rate (SE): none							
<b>PPA at 2 y</b>							
NRT vs. placebo (3)		0.566 (0.203)	1.76	1.17-2.64	0.590 (0.443)	1.80	0.74-4.38
P(placebo is best)	6.6						
P (NRT is best)	93.4						

**Appendix 8a: NRT vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Placebo rate (SE): 0.123 (0.093)							
<b>Relapse at 1 y<sup>§</sup></b>							
NRT vs. placebo (26)		0.793 (0.060)	2.21	1.96-2.49	0.811 (0.071)	2.25	1.95-2.60
Bupropion vs. placebo (6)		0.746 (0.124)	2.11	1.64-2.70	0.763 (0.142)	2.15	1.62-2.85
Varenicline vs. placebo (6)		1.114 (0.097)	3.05	2.51-3.70	1.119 (0.110)	3.06	2.45-3.82
Bupropion vs. NRT (0)		-0.048 (0.138)	0.95	0.72-1.26	-0.048 (0.149)	0.95	0.71-1.28
Varenicline vs. NRT (1)		0.320 (0.114)	1.38	1.10-1.73	0.307 (0.118)	1.36	1.07-1.72
Varenicline vs. Bupropion (3)		0.368 (0.158)	1.45	1.05-1.98	0.355 (0.140)	1.43	1.08-1.89
P(placebo is worst)	0.0						
P (NRT is worst)	0.7						
P (Bupropion is worst)	0.8						
P (Varenicline is worst)	98.5						
Placebo rate (SE): 0.062 (0.007)							

§ relapse = proportion of quitters at 3 months was detected as smokers at 1 year

CAR: continuous abstinence rate; CI: confidence interval; CrI: credible interval; m: month; OR: odds ratio; P: probability; PAR: prolonged abstinence rate; PPA: point prevalence abstinence; SE: standard error; y: year

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<i>CAR at 6 m</i>							
Patch vs. placebo (11)		0.730 (0.071)	2.07	1.80-2.39	0.784 (0.097)	2.19	1.80-2.66
Bupropion vs. placebo (10)		0.673 (0.088)	1.96	1.64-2.34	0.703 (0.113)	2.02	1.61-2.53
Gum vs. placebo (6)		0.794 (0.083)	2.21	1.88-2.61	0.808 (0.134)	2.24	1.72-2.93
Spray vs. placebo (4)		0.922 (0.148)	2.51	1.87-3.38	0.935 (0.163)	2.55	1.84-3.53
Varenicline vs. placebo (7)		0.974 (0.079)	2.65	2.26-3.10	0.981 (0.101)	2.67	2.18-3.26
Inhaler vs. placebo (3)		0.776 (0.195)	2.17	1.47-3.21	0.774 (0.218)	2.17	1.40-3.35
Sublingual vs. placebo (2)		0.817 (0.234)	2.26	1.42-3.62	0.837 (0.268)	2.31	1.35-3.95
Lozenge vs. placebo (1)		0.803 (0.127)	2.23	1.73-2.88	0.797 (0.219)	2.22	1.43-3.44
Bupropion vs. patch (0)		-0.057 (0.113)	0.94	0.75-1.18	-0.081 (0.143)	0.92	0.69-1.23
Gum vs. patch (0)		0.065 (0.109)	1.07	0.86-1.33	0.024 (0.160)	1.02	0.74-1.41
Spray vs. patch (1)		0.192 (0.165)	1.21	0.87-1.68	0.151 (0.176)	1.16	0.82-1.65
Varenicline vs. patch (1)		0.245 (0.107)	1.28	1.03-1.58	0.197 (0.127)	1.22	0.95-1.57
Inhaler vs. patch (0)		0.047 (0.207)	1.05	0.69-1.59	-0.010 (0.242)	0.99	0.61-1.61
Sublingual vs. patch (0)		0.088 (0.245)	1.09	0.67-1.78	0.053 (0.285)	1.05	0.60-1.86
Lozenge vs. patch (0)		0.073 (0.146)	1.08	0.80-1.44	0.013 (0.240)	1.01	0.63-1.64
Gum vs. bupropion (0)		0.122 (0.121)	1.13	0.89-1.44	0.105 (0.179)	1.11	0.78-1.59
Spray vs. bupropion (0)		0.249 (0.173)	1.28	0.91-1.81	0.232 (0.198)	1.26	0.85-1.87
Varenicline vs. bupropion (3)		0.302 (0.118)	1.35	1.07-1.71	0.278 (0.130)	1.32	1.02-1.71
Inhaler vs. bupropion (0)		0.103 (0.214)	1.11	0.72-1.70	0.070 (0.251)	1.07	0.65-1.77
Sublingual vs. bupropion (0)		0.145 (0.250)	1.16	0.70-1.91	0.134 (0.295)	1.14	0.63-2.06
Lozenge vs. bupropion (0)		0.130 (0.155)	1.14	0.84-1.55	0.094 (0.245)	1.10	0.67-1.79
Spray vs. gum (1)		0.127 (0.170)	1.14	0.81-1.60	0.127 (0.210)	1.14	0.75-1.73
Varenicline vs. gum (0)		0.180 (0.115)	1.20	0.95-1.51	0.173 (0.165)	1.19	0.85-1.65
Inhaler vs. gum (1)		-0.018 (0.212)	0.98	0.64-1.50	-0.034 (0.257)	0.97	0.58-1.62
Sublingual vs. gum (0)		0.023 (0.249)	1.02	0.62-1.68	0.029 (0.299)	1.03	0.57-1.87
Lozenge vs. gum (0)		0.008 (0.152)	1.01	0.74-1.37	-0.011 (0.264)	0.99	0.58-1.68
Varenicline vs. spray (0)		0.053 (0.168)	1.05	0.75-1.48	0.046 (0.192)	1.05	0.71-1.54

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Inhaler vs. spray (1)		-0.146 (0.245)	0.86	0.53-1.41	-0.161 (0.263)	0.85	0.50-1.44
Sublingual vs. spray (0)		-0.104 (0.278)	0.90	0.52-1.57	-0.098 (0.316)	0.91	0.48-1.71
Lozenge vs. spray (0)		-0.119 (0.196)	0.89	0.60-1.31	-0.138 (0.281)	0.87	0.50-1.53
Inhaler vs. varenicline (0)		-0.198 (0.210)	0.82	0.54-1.25	-0.208 (0.243)	0.81	0.50-1.32
Sublingual vs. varenicline (0)		-0.157 (0.248)	0.85	0.52-1.40	-0.144 (0.292)	0.87	0.48-1.55
Lozenge vs. varenicline (0)		-0.172 (0.150)	0.84	0.62-1.14	-0.184 (0.234)	0.83	0.52-1.33
Sublingual vs. inhaler (0)		0.041 (0.305)	1.04	0.57-1.92	0.064 (0.344)	1.07	0.54-2.12
Lozenge vs. inhaler (0)		0.027 (0.233)	1.03	0.64-1.64	0.024 (0.311)	1.02	0.55-1.91
Lozenge vs. sublingual (0)		-0.015 (0.267)	0.99	0.58-1.68	-0.040 (0.339)	0.96	0.49-1.89
P(placebo is best)	0.0						
P(patch is best)	0.9						
P(bupropion is best)	0.2						
P(gum is best)	4.1						
P(spray is best)	24.3						
P(varenicline is best)	29.5						
P(inhaler is best)	9.8						
P(sublingual is best)	20.8						
P(lozenge is best)	10.4						
<b>CAR at 1 y</b>							
Patch vs. placebo (12)		0.527 (0.072)	1.69	1.47-1.96	0.573 (0.102)	1.77	1.45-2.18
Gum vs. placebo (6)		0.493 (0.124)	1.64	1.28-2.10	0.518 (0.146)	1.68	1.25-2.25
Bupropion vs. placebo (9)		0.624 (0.089)	1.87	1.56-2.23	0.657 (0.120)	1.93	1.52-2.45
Inhaler vs. placebo (4)		0.788 (0.214)	2.20	1.43-3.37	0.807 (0.240)	2.24	1.39-3.63
Spray vs. placebo (4)		0.854 (0.185)	2.35	1.62-3.40	0.865 (0.219)	2.38	1.53-3.68
Varenicline vs. placebo (6)		0.970 (0.092)	2.64	2.19-3.17	1.004 (0.126)	2.73	2.12-3.51
Sublingual vs. placebo (2)		0.584 (0.250)	1.79	1.09-2.95	0.587 (0.294)	1.80	1.00-3.24
Lozenge vs. placebo (1)		0.824 (0.152)	2.28	1.68-3.09	0.838 (0.253)	2.31	1.39-3.83
Gum vs. patch (0)		-0.034 (0.144)	0.97	0.72-1.29	-0.055 (0.173)	0.95	0.67-1.34

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Bupropion vs. patch (1)		0.097 (0.115)	1.10	0.88-1.39	0.084 (0.143)	1.09	0.82-1.45
Inhaler vs. patch (0)		0.261 (0.226)	1.30	0.83-2.04	0.235 (0.259)	1.26	0.75-2.12
Spray vs. patch (0)		0.237 (0.199)	1.39	0.93-2.07	0.292 (0.246)	1.34	0.82-2.19
Varenicline vs. patch (1)		0.443 (0.117)	1.56	1.23-1.97	0.430 (0.146)	1.54	1.15-2.06
Sublingual vs. patch (0)		0.057 (0.260)	1.06	0.63-1.78	0.014 (0.309)	1.01	0.55-1.88
Lozenge vs. patch (0)		0.297 (0.168)	1.35	0.96-1.88	0.264 (0.271)	1.30	0.76-2.24
Bupropion vs. Gum (0)		0.131 (0.153)	1.14	0.84-1.55	0.139 (0.189)	1.15	0.79-1.68
Inhaler vs. Gum (0)		0.295 (0.247)	1.34	0.82-2.20	0.290 (0.279)	1.34	0.77-2.33
Spray vs. gum (0)		0.316 (0.223)	1.44	0.92-2.24	0.347 (0.260)	1.41	0.84-2.38
Varenicline vs. gum (0)		0.477 (0.155)	1.61	1.18-2.20	0.486 (0.191)	1.63	1.11-2.38
Sublingual vs. gum (0)		0.091 (0.279)	1.10	0.63-1.91	0.069 (0.321)	1.07	0.56-2.04
Lozenge vs. gum (0)		0.331 (0.196)	1.39	0.94-2.06	0.320 (0.288)	1.38	0.77-2.45
Inhaler vs. bupropion (0)		0.164 (0.232)	1.18	0.74-1.87	0.151 (0.268)	1.16	0.68-1.99
Spray vs. bupropion (0)		0.230 (0.206)	1.26	0.83-1.90	0.208 (0.257)	1.23	0.74-2.06
Varenicline vs. bupropion (3)		0.346 (0.128)	1.41	1.09-1.83	0.346 (0.145)	1.41	1.06-1.89
Sublingual vs. bupropion (0)		-0.040 (0.265)	0.96	0.57-1.63	-0.070 (0.318)	0.93	0.49-1.76
Lozenge vs. bupropion (0)		0.200 (0.176)	1.22	0.86-1.74	0.180 (0.284)	1.20	0.68-2.11
Spray vs. inhaler (0)		0.066 (0.283)	1.07	0.61-1.88	0.057 (0.321)	1.06	0.56-2.01
Varenicline vs. inhaler (0)		0.182 (0.233)	1.20	0.75-1.91	0.196 (0.268)	1.22	0.71-2.08
Sublingual vs. inhaler (0)		-0.204 (0.329)	0.82	0.42-1.57	-0.221 (0.361)	0.80	0.39-1.65
Lozenge vs. inhaler (0)		0.036 (0.263)	1.04	0.61-1.75	0.030 (0.347)	1.03	0.51-2.06
Varenicline vs. spray (0)		0.116 (0.207)	1.12	0.74-1.70	0.138 (0.253)	1.15	0.69-1.90
Sublingual vs. spray (0)		-0.270 (0.311)	0.76	0.41-1.42	-0.278 (0.371)	0.76	0.36-1.59
Lozenge vs. spray (0)		-0.030 (0.240)	0.97	0.60-1.57	-0.027 (0.334)	0.97	0.50-1.90
Sublingual vs. varenicline (0)		-0.386 (0.266)	0.68	0.40-1.16	-0.416 (0.319)	0.66	0.35-1.25
Lozenge vs. varenicline (0)		-0.146 (0.178)	0.86	0.61-1.23	-0.166 (0.287)	0.85	0.48-1.50
Lozenge vs. sublingual (0)		0.240 (0.292)	1.27	0.71-2.28	0.250 (0.393)	1.28	0.59-2.82
P(placebo is best)	0.0						

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(patch is best)	0.0						
P(gum is best)	0.0						
P(bupropion is best)	0.2						
P(inhaler is best)	14.4						
P(spray is best)	19.1						
P(varenicline is best)	42.4						
P(sublingual is best)	5.8						
P(lozenge is best)	18.1						
<b>CAR at 2 y</b>							
Gum vs. placebo (2)		0.856 (0.280)	2.35	1.34-4.12	0.971 (0.702)	2.64	0.65-10.75
Patch vs. placebo (2)		1.376 (0.340)	3.96	2.01-7.81	1.558 (0.811)	4.75	0.94-24.04
Inhaler vs. placebo (1)		1.401 (1.123)	4.06	0.43-38.34	1.804 (1.663)	6.07	0.22-169.05
Spray vs. placebo (1)		0.356 (0.434)	1.43	0.60-3.40	0.352 (1.017)	1.42	0.19-10.87
Patch vs. gum (0)		0.520 (0.440)	1.68	0.70-4.06	0.587 (1.092)	1.80	0.20-15.98
Inhaler vs. gum (0)		0.545 (1.157)	1.73	0.17-17.45	0.834 (1.822)	2.30	0.06-88.00
Spray vs. gum (0)		-0.500 (0.516)	0.61	0.22-1.70	-0.619 (1.237)	0.54	0.05-6.39
Inhaler vs. patch (0)		0.026 (1.173)	1.03	0.10-10.71	0.246 (1.886)	1.28	0.03-55.61
Spray vs. patch (0)		-1.020 (0.551)	0.36	0.12-1.09	-1.206 (1.234)	0.30	0.03-3.53
Spray vs. Inhaler (0)		-1.046 (1.203)	0.35	0.03-3.90	-1.452 (1.986)	0.23	0.00-12.43
P(placebo is best)	0.1						
P(gum is best)	11.2						
P(patch is best)	35.6						
P(inhaler is best)	49.3						
P(spray is best)	3.8						
<b>CAR at 3 y</b>							
Patch vs. placebo (2)		1.191 (0.345)	3.29	1.65-6.56	1.258 (0.706)	3.52	0.86-14.43
P(placebo is best)	3.1						
P (patch is best)	96.9						

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b><i>CAR at 4 y</i></b>							
Gum vs. placebo (1)		0.002 (0.266)	1.00	0.59-1.71	-0.008 (0.261)	0.99	0.59-1.67
P(placebo is best)	50.9						
P (Gum is best)	49.1						
<b><i>CAR at 5 y</i></b>							
Patch vs. placebo (2)		0.574 (0.302)	1.78	0.97-3.25	0.543 (0.731)	1.72	0.40-7.43
P(placebo is best)	17.1						
P (patch is best)	82.9						
<b><i>CAR at 7 y</i></b>							
Patch vs. placebo (1)		1.478 (0.571)	4.38	1.40-13.74	1.424 (0.588)	4.15	1.28-13.45
P(placebo is best)	0.5						
P (patch is best)	99.5						
<b><i>CAR at 8 y</i></b>							
Patch vs. placebo (1)		0.326 (0.228)	1.39	0.88-2.19	0.317 (0.230)	1.37	0.87-2.18
P(placebo is best)	8.7						
P (patch is best)	91.3						
<b><i>CAR at 10 y</i></b>							
Patch vs. placebo (1)		1.161 (0.589)	3.19	0.98-10.37	1.090 (0.577)	2.97	0.94-9.43
P(placebo is best)	2.5						
P (patch is best)	97.5						
<b><i>PAR at 6 m</i></b>							
Bupropion vs. placebo (1)		0.580 (0.227)	1.79	1.13-2.81	0.554 (1.172)	1.74	0.17-18.16
Spray vs. placebo (1)		0.794 (0.276)	2.21	1.27-3.84	0.811 (1.155)	2.25	0.22-22.66
Patch vs. placebo (0)		0.997 (0.381)	2.71	1.27-5.81	1.084 (1.682)	2.96	0.10-85.43
Spray vs. bupropion (0)		0.214 (0.357)	1.24	0.61-2.53	0.257 (1.593)	1.29	0.05-31.28
Patch vs. bupropion (0)		0.417 (0.443)	1.52	0.63-3.68	0.530 (2.057)	1.70	0.03-104.05
Patch vs. spray (1)		0.203 (0.470)	1.23	0.48-3.14	0.273 (1.206)	1.31	0.12-14.65
P(placebo is best)	4.4						

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P (bupropion is best)	25.4						
P (spray is best)	19.7						
P(patch is best)	50.5						
<b>PAR at 1 y</b>							
Spray vs. placebo (2)		0.776 (0.231)	2.17	1.37-3.45	0.821 (0.651)	2.27	0.62-8.36
Bupropion vs. placebo (1)		0.443 (0.256)	1.56	0.93-2.60	0.458 (0.931)	1.58	0.25-10.17
Gum vs. placebo (1)		1.202 (0.452)	3.33	1.35-8.22	1.233 (0.995)	3.43	0.47-25.12
Patch vs. placebo (1)		0.909 (0.320)	2.48	1.31-4.71	0.979 (0.934)	2.66	0.41-17.24
Varenicline vs. placebo (1)		0.774 (0.234)	2.17	1.36-3.47	0.778 (0.888)	2.18	0.37-12.84
Bupropion vs. spray (0)		-0.333 (0.344)	0.72	0.36-1.43	-0.363 (1.122)	0.70	0.07-6.56
Gum vs. spray (0)		0.426 (0.508)	1.53	0.55-4.23	0.411 (1.232)	1.51	0.13-17.75
Patch vs. spray (0)		0.133 (0.395)	1.14	0.52-2.52	0.158 (1.133)	1.17	0.12-11.29
Varenicline vs. spray (0)		-0.002 (0.329)	1.00	0.52-1.93	-0.043 (1.101)	0.96	0.11-8.65
Gum vs. bupropion (0)		0.759 (0.520)	2.14	0.76-6.04	0.775 (1.399)	2.17	0.13-35.63
Patch vs. bupropion (0)		0.466 (0.410)	1.59	0.70-3.62	0.521 (1.268)	1.68	0.13-21.26
Varenicline vs. bupropion (0)		0.331 (0.347)	1.39	0.70-2.79	0.320 (1.326)	1.38	0.10-19.51
Patch vs. gum (0)		-0.293 (0.554)	0.75	0.25-2.26	-0.254 (1.274)	0.78	0.06-9.91
Varenicline vs. gum (0)		-0.428 (0.510)	0.65	0.24-1.81	-0.455 (1.385)	0.63	0.04-10.12
Varenicline vs. patch (0)		-0.135 (0.397)	0.87	0.39-1.93	-0.201 (1.287)	0.82	0.06-10.73
P(placebo is best)	0.0						
P(spray is best)	12.2						
P(bupropion is best)	8.1						
P(gum is best)	41.7						
P(patch is best)	23.0						
P(varenicline is best)	15.0						
<b>PPA at 6 m</b>							
Bupropion vs. placebo (13)		0.636 (0.060)	1.89	1.68-2.13	0.640 (0.076)	1.90	1.63-2.21
Gum vs. placebo (9)		0.501 (0.104)	1.65	1.34-2.03	0.511 (0.116)	1.67	1.32-2.10

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Patch vs. placebo (6)		0.583 (0.093)	1.79	1.49-2.16	0.594 (0.111)	1.81	1.45-2.26
Varenicline vs. placebo (4)		0.983 (0.086)	2.67	2.25-3.18	1.001 (0.108)	2.72	2.19-3.38
Inhaler vs. placebo (1)		0.977 (0.287)	2.66	1.50-4.72	0.986 (0.307)	2.68	1.45-4.95
Spray vs. placebo (0)		0.419 (0.202)	1.52	1.02-2.28	0.418 (0.223)	1.52	0.97-2.37
Lozenge vs. placebo (0)		0.713 (0.350)	2.04	1.01-4.11	0.738 (0.393)	2.09	0.95-4.60
Gum vs. bupropion (0)		-0.135 (0.120)	0.87	0.69-1.11	-0.130 (0.140)	0.88	0.66-1.16
Patch vs. bupropion (2)		-0.053 (0.110)	0.95	0.76-1.18	-0.046 (0.119)	0.95	0.75-1.21
Varenicline vs. bupropion (2)		0.347 (0.105)	1.42	1.15-1.75	0.360 (0.112)	1.43	1.15-1.79
Inhaler vs. bupropion (0)		0.341 (0.293)	1.41	0.78-2.53	0.345 (0.316)	1.41	0.75-2.66
Spray vs. bupropion (0)		-0.217 (0.210)	0.80	0.53-1.23	-0.222 (0.224)	0.80	0.51-1.25
Lozenge vs. bupropion (0)		0.077 (0.355)	1.08	0.53-2.20	0.098 (0.405)	1.10	0.49-2.48
Patch vs. gum (0)		0.082 (0.139)	1.09	0.82-1.43	0.084 (0.163)	1.09	0.78-1.51
Varenicline vs. gum (0)		0.482 (0.135)	1.62	1.24-2.12	0.490 (0.161)	1.63	1.18-2.25
Inhaler vs. gum (1)		0.476 (0.305)	1.61	0.87-2.96	0.475 (0.323)	1.61	0.84-3.07
Spray vs. gum (1)		-0.082 (0.227)	0.92	0.59-1.45	-0.093 (0.255)	0.91	0.55-1.52
Lozenge vs. gum (1)		0.212 (0.365)	1.24	0.60-2.56	0.228 (0.370)	1.26	0.60-2.63
Varenicline vs. patch (1)		0.400 (0.127)	1.49	1.16-1.92	0.406 (0.135)	1.50	1.15-1.96
Inhaler vs. patch (0)		0.394 (0.302)	1.48	0.81-2.71	0.392 (0.322)	1.48	0.78-2.82
Spray vs. patch (2)		-0.164 (0.222)	0.85	0.54-1.32	-0.176 (0.199)	0.84	0.56-1.25
Lozenge vs. patch (0)		0.130 (0.362)	1.14	0.55-2.35	0.144 (0.413)	1.16	0.51-2.64
Inhaler vs. varenicline (0)		-0.006 (0.300)	0.99	0.55-1.81	-0.015 (0.323)	0.99	0.52-1.88
Spray vs. varenicline (0)		-0.564 (0.219)	0.57	0.37-0.88	-0.583 (0.231)	0.56	0.35-0.89
Lozenge vs. varenicline (0)		-0.271 (0.361)	0.76	0.37-1.57	-0.262 (0.412)	0.77	0.34-1.75
Spray vs. inhaler (1)		-0.558 (0.351)	0.57	0.28-1.15	-0.568 (0.355)	0.57	0.28-1.15
Lozenge vs. inhaler (0)		-0.264 (0.453)	0.77	0.31-1.90	-0.248 (0.492)	0.78	0.29-2.09
Lozenge vs. spray (0)		0.294 (0.404)	1.34	0.60-3.01	0.320 (0.455)	1.38	0.55-3.42
P(placebo is best)	0.0						
P(bupropion is best)	0.0						

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(gum is best)	0.0						
P(patch is best)	0.1						
P(varenicline is best)	38.6						
P(inhaler is best)	41.6						
P(spray is best)	0.0						
P(lozenge is best)	19.7						
<b>PPA at 1 y</b>							
Gum vs. placebo (9)		0.730 (0.123)	2.07	1.62-2.65	0.729 (0.157)	2.07	1.51-2.84
Bupropion vs. placebo (10)		0.587 (0.069)	1.80	1.57-2.06	0.599 (0.112)	1.82	1.46-2.28
Patch vs. placebo (5)		0.506 (0.099)	1.66	1.36-2.02	0.522 (0.160)	1.68	1.22-2.32
Inhaler vs. placebo (3)		0.899 (0.244)	2.46	1.51-4.01	0.938 (0.302)	2.56	1.40-4.68
Varenicline vs. placebo (5)		0.855 (0.084)	2.35	1.99-2.78	0.900 (0.139)	2.46	1.86-3.25
Lozenge vs. placebo (0)		1.051 (0.387)	2.86	1.32-6.20	1.064 (0.492)	2.90	1.08-7.75
Bupropion vs. gum (0)		-0.143 (0.141)	0.87	0.65-1.15	-0.131 (0.193)	0.88	0.60-1.29
Patch vs. gum (0)		-0.223 (0.158)	0.80	0.58-1.10	-0.208 (0.224)	0.81	0.52-1.27
Inhaler vs. gum (0)		0.170 (0.274)	1.18	0.69-2.05	0.209 (0.339)	1.23	0.63-2.43
Varenicline vs. gum (0)		0.126 (0.149)	1.13	0.84-1.53	0.170 (0.211)	1.19	0.78-1.81
Lozenge vs. gum (1)		0.321 (0.406)	1.38	0.61-3.11	0.334 (0.470)	1.40	0.55-3.57
Patch vs. bupropion (1)		-0.081 (0.120)	0.92	0.73-1.17	-0.077 (0.186)	0.93	0.64-1.34
Inhaler vs. bupropion (0)		0.312 (0.254)	1.37	0.82-2.27	0.340 (0.324)	1.40	0.74-2.68
Varenicline vs. bupropion (2)		0.268 (0.109)	1.31	1.05-1.63	0.301 (0.164)	1.35	0.97-1.88
Lozenge vs. Bupropion (0)		0.464 (0.393)	1.59	0.72-3.49	0.465 (0.500)	1.59	0.59-4.33
Inhaler vs. patch (0)		0.393 (0.264)	1.48	0.87-2.51	0.417 (0.339)	1.52	0.77-2.99
Varenicline vs. Patch (1)		0.349 (0.130)	1.42	1.09-1.84	0.378 (0.191)	1.46	1.00-2.14
Lozenge vs. patch (0)		0.545 (0.400)	1.72	0.78-3.83	0.542 (0.518)	1.72	0.61-4.84
Varenicline vs. inhaler (0)		-0.044 (0.258)	0.96	0.57-1.60	-0.039 (0.329)	0.96	0.50-1.86
Lozenge vs. inhaler (0)		0.152 (0.458)	1.16	0.47-2.91	0.125 (0.579)	1.13	0.36-3.61
Lozenge vs. varenicline (0)		0.196 (0.396)	1.22	0.55-2.69	0.164 (0.516)	1.18	0.42-3.31

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(placebo is best)	0.0						
P(gum is best)	2.2						
P(bupropion is best)	0.0						
P(patch is best)	0.4						
P(inhaler is best)	28.1						
P(varenicline is best)	17.7						
P(lozenge is best)	51.6						
<b>PPA at 15 m</b>							
Inhaler vs. placebo (1)		1.798 (0.634)	6.04	1.70-21.46	1.727 (0.621)	5.62	1.62-19.47
P(placebo is best)	0.1						
P (inhaler is best)	99.9						
<b>PPA at 2 y</b>							
Gum vs. placebo (2)		0.740 (0.252)	2.10	1.27-3.47	0.794 (0.726)	2.21	0.52-9.45
Inhaler vs. placebo (1)		0.233 (0.343)	1.26	0.64-2.51	0.291 (1.020)	1.34	0.17-10.28
Inhaler vs. gum (0)		-0.506 (0.426)	0.60	0.26-1.41	-0.503 (1.207)	0.60	0.05-6.76
P(placebo is best)	3.6						
P(gum is best)	72.1						
P(inhaler is best)	24.3						
<b>Relapse at 1 y<sup>§</sup></b>							
Patch vs. placebo (11)		0.793 (0.081)	2.21	1.88-2.60	0.820 (0.098)	2.27	1.87-2.76
Gum vs. placebo (5)		0.645 (0.163)	1.91	1.38-2.64	0.651 (0.181)	1.92	1.33-2.76
Spray vs. placebo (4)		1.113 (0.248)	3.04	1.85-5.00	1.140 (0.255)	3.13	1.88-5.21
Bupropion vs. placebo (6)		0.746 (0.125)	2.11	1.64-2.70	0.770 (0.138)	2.16	1.64-2.85
Inhaler vs. placebo (3)		0.799 (0.332)	2.22	1.14-4.32	0.825 (0.347)	2.28	1.14-4.57
Varenicline vs. placebo (6)		1.114 (0.099)	3.05	2.50-3.71	1.125 (0.116)	3.08	2.44-3.89
Sublingual vs. placebo (2)		1.004 (0.305)	2.73	1.48-5.02	1.010 (0.326)	2.75	1.43-5.27
Lozenge vs. placebo (1)		0.724 (0.140)	2.06	1.56-2.73	0.728 (0.202)	2.07	1.38-3.10
Gum vs. patch (0)		-0.148 (0.182)	0.86	0.60-1.24	-0.169 (0.204)	0.84	0.56-1.27

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Spray vs. patch (0)		0.320 (0.261)	1.38	0.82-2.32	0.320 (0.268)	1.38	0.81-2.35
Bupropion vs. patch (0)		-0.048 (0.149)	0.95	0.71-1.28	-0.050 (0.157)	0.95	0.69-1.30
Inhaler vs. patch (0)		0.005 (0.342)	1.01	0.51-1.99	0.004 (0.358)	1.00	0.49-2.06
Varenicline vs. patch (1)		0.321 (0.128)	1.38	1.07-1.78	0.305 (0.135)	1.36	1.03-1.78
Sublingual vs. patch (0)		0.210 (0.315)	1.23	0.66-2.32	0.190 (0.347)	1.21	0.60-2.42
Lozenge vs. patch (0)		-0.069 (0.162)	0.93	0.68-1.29	-0.092 (0.216)	0.91	0.59-1.40
Spray vs. gum (0)		0.468 (0.297)	1.60	0.88-2.89	0.489 (0.311)	1.63	0.88-3.04
Bupropion vs. gum (0)		0.100 (0.205)	1.11	0.73-1.67	0.119 (0.225)	1.13	0.72-1.77
Inhaler vs. gum (0)		0.153 (0.370)	1.17	0.56-2.44	0.174 (0.398)	1.19	0.54-2.64
Varenicline vs. gum (0)		0.469 (0.191)	1.60	1.09-2.34	0.474 (0.214)	1.61	1.05-2.46
Sublingual vs. gum (0)		0.358 (0.345)	1.43	0.72-2.86	0.359 (0.372)	1.43	0.68-3.01
Lozenge vs. gum (0)		0.079 (0.215)	1.08	0.70-1.66	0.077 (0.266)	1.08	0.63-1.84
Bupropion vs. spray (0)		-0.367 (0.278)	0.69	0.40-1.21	-0.370 (0.285)	0.69	0.39-1.22
Inhaler vs. spray (0)		-0.314 (0.415)	0.73	0.32-1.67	-0.316 (0.432)	0.73	0.31-1.73
Varenicline vs. spray (0)		0.001 (0.267)	1.00	0.59-1.71	-0.015 (0.276)	0.98	0.57-1.71
Sublingual vs. spray (0)		-0.109 (0.393)	0.90	0.41-1.97	-0.130 (0.416)	0.88	0.38-2.02
Lozenge vs. spray (0)		-0.389 (0.285)	0.68	0.38-1.20	-0.412 (0.330)	0.66	0.34-1.28
Inhaler vs. bupropion (0)		0.053 (0.355)	1.05	0.52-2.14	0.054 (0.369)	1.06	0.51-2.21
Varenicline vs. bupropion (3)		0.368 (0.159)	1.45	1.05-1.99	0.355 (0.140)	1.43	1.08-1.89
Sublingual vs. bupropion (0)		0.258 (0.329)	1.29	0.67-2.50	0.240 (0.359)	1.27	0.62-2.61
Lozenge vs. bupropion (0)		-0.021 (0.188)	0.98	0.67-1.42	-0.042 (0.246)	0.96	0.59-1.57
Varenicline vs. inhaler (0)		0.315 (0.347)	1.37	0.69-2.74	0.300 (0.364)	1.35	0.65-2.79
Sublingual vs. inhaler (0)		0.205 (0.451)	1.23	0.50-3.02	0.186 (0.469)	1.20	0.47-3.07
Lozenge vs. inhaler (0)		-0.074 (0.361)	0.93	0.45-1.91	-0.097 (0.414)	0.91	0.40-2.08
Sublingual vs. varenicline (0)		-0.110 (0.320)	0.90	0.47-1.70	-0.115 (0.347)	0.89	0.45-1.79
Lozenge vs. varenicline (0)		-0.390 (0.171)	0.68	0.48-0.95	-0.397 (0.232)	0.67	0.42-1.07
Lozenge vs. sublingual (0)		-0.279 (0.335)	0.76	0.39-1.48	-0.282 (0.390)	0.75	0.35-1.64
P(placebo is worst)	0.0						

**Appendix 8b: NRTs broken down vs. bupropion vs. varenicline vs. placebo in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(patch is worst)	0.0						
P(gum is worst)	0.2						
P(spray is worst)	37.4						
P(bupropion is worst)	0.0						
P(inhaler is worst)	12.2						
P(varenicline is worst)	25.8						
P(sublingual is worst)	22.9						
P(lozenge is worst)	1.5						

§ relapse = proportion of quitters at 3 months was detected as smokers at 1 year

CAR: continuous abstinence rate; CI: confidence interval; CrI: credible interval; m: month; OR: odds ratio; P: probability; PAR: prolonged abstinence rate; PPA: point prevalence abstinence; SE: standard error; y: year

Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>CAR at 6 m</b>							
Patch vs. placebo (11)		0.730 (0.077)	2.07	1.78-2.42	0.775 (0.099)	2.17	1.78-2.65
Gum vs. placebo (6)		0.794 (0.083)	2.21	1.88-2.61	0.803 (0.122)	2.23	1.75-2.85
Spray vs. placebo (4)		0.922 (0.149)	2.51	1.87-3.38	0.939 (0.164)	2.56	1.84-3.55
Inhaler vs. placebo (3)		0.776 (0.195)	2.17	1.47-3.21	0.782 (0.220)	2.19	1.41-3.39
Sublingual vs. placebo (2)		0.817 (0.234)	2.26	1.42-3.62	0.826 (0.266)	2.29	1.34-3.89
Lozenge vs. placebo (1)		0.803 (0.127)	2.23	1.73-2.88	0.810 (0.197)	2.25	1.52-3.34
Gum vs. patch (0)		0.065 (0.113)	1.07	0.85-1.34	0.028 (0.152)	1.03	0.76-1.39
Spray vs. patch (1)		0.192 (0.168)	1.21	0.87-1.69	0.164 (0.178)	1.18	0.83-1.68
Inhaler vs. patch (0)		0.046 (0.210)	1.05	0.69-1.59	0.006 (0.240)	1.01	0.62-1.63
Sublingual vs. patch (0)		0.087 (0.247)	1.09	0.67-1.79	0.051 (0.284)	1.05	0.60-1.86
Lozenge vs. patch (0)		0.073 (0.149)	1.08	0.80-1.45	0.035 (0.221)	1.04	0.67-1.61
Spray vs. gum (1)		0.127 (0.170)	1.14	0.81-1.60	0.135 (0.202)	1.15	0.76-1.72
Inhaler vs. gum (1)		-0.018 (0.212)	0.98	0.64-1.50	-0.022 (0.251)	0.98	0.59-1.62
Sublingual vs. gum (0)		0.023 (0.249)	1.02	0.62-1.68	0.023 (0.291)	1.02	0.57-1.83
Lozenge vs. gum (0)		0.008 (0.152)	1.01	0.74-1.37	0.007 (0.227)	1.01	0.64-1.59
Inhaler vs. spray (1)		-0.146 (0.245)	0.86	0.53-1.41	-0.157 (0.265)	0.85	0.50-1.45
Sublingual vs. spray (0)		-0.104 (0.278)	0.90	0.52-1.57	-0.112 (0.314)	0.89	0.48-1.68
Lozenge vs. spray (0)		-0.119 (0.196)	0.89	0.60-1.31	-0.129 (0.261)	0.88	0.52-1.48
Sublingual vs. inhaler (0)		0.041 (0.305)	1.04	0.57-1.92	0.045 (0.345)	1.05	0.53-2.08
Lozenge vs. inhaler (0)		0.027 (0.233)	1.03	0.64-1.64	0.028 (0.293)	1.03	0.57-1.85
Lozenge vs. sublingual (0)		-0.015 (0.267)	0.99	0.58-1.68	-0.016 (0.327)	0.98	0.51-1.89
P(placebo is best)	0.0						
P(patch is best)	3.0						
P(gum is best)	7.8						
P(spray is best)	37.5						
P(inhaler is best)	13.7						
P(sublingual is best)	23.4						
P(lozenge is best)	14.6						

**Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Placebo rate (SE): 0.112 (0.010)							
<b><i>CAR at 1 y</i></b>							
Patch vs. placebo (12)		0.552 (0.080)	1.74	1.48-2.04	0.589 (0.102)	1.80	1.47-2.21
Gum vs. placebo (6)		0.493 (0.124)	1.64	1.28-2.10	0.512 (0.148)	1.67	1.24-2.24
Inhaler vs. placebo (4)		0.788 (0.214)	2.20	1.43-3.37	0.797 (0.237)	2.22	1.38-3.57
Spray vs. placebo (4)		0.854 (0.185)	2.35	1.62-3.40	0.856 (0.202)	2.35	1.57-3.53
Sublingual vs. placebo (2)		0.584 (0.250)	1.79	1.09-2.95	0.582 (0.271)	1.79	1.04-3.08
Lozenge vs. placebo (1)		0.824 (0.152)	2.28	1.68-3.09	0.832 (0.225)	2.30	1.47-3.60
Gum vs. patch (0)		-0.059 (0.147)	0.94	0.70-1.27	-0.078 (0.179)	0.93	0.65-1.32
Inhaler vs. patch (0)		0.236 (0.228)	1.27	0.80-2.00	0.208 (0.259)	1.23	0.73-2.07
Spray vs. patch (0)		0.302 (0.202)	1.35	0.90-2.03	0.267 (0.229)	1.31	0.83-2.07
Sublingual vs. patch (0)		0.032 (0.262)	1.03	0.61-1.74	-0.007 (0.288)	0.99	0.56-1.77
Lozenge vs. patch (0)		0.272 (0.172)	1.31	0.93-1.85	0.242 (0.245)	1.27	0.78-2.08
Inhaler vs. gum (0)		0.295 (0.247)	1.34	0.82-2.20	0.286 (0.281)	1.33	0.76-2.33
Spray vs. gum (0)		0.361 (0.223)	1.44	0.92-2.24	0.344 (0.249)	1.41	0.86-2.32
Sublingual vs. gum (0)		0.091 (0.279)	1.10	0.63-1.91	0.070 (0.308)	1.07	0.58-1.99
Lozenge vs. gum (0)		0.331 (0.196)	1.39	0.94-2.06	0.320 (0.65)	1.38	0.81-2.34
Spray vs. inhaler (0)		0.066 (0.283)	1.07	0.61-1.88	0.059 (0.311)	1.06	0.57-1.98
Sublingual vs. inhaler (0)		-0.204 (0.329)	0.82	0.42-1.57	-0.215 (0.364)	0.81	0.39-1.67
Lozenge vs. inhaler (0)		0.036 (0.263)	1.04	0.61-1.75	0.034 (0.321)	1.03	0.55-1.96
Sublingual vs. spray (0)		-0.270 (0.311)	0.76	0.41-1.42	-0.274 (0.342)	0.76	0.38-1.51
Lozenge vs. spray (0)		-0.030 (0.240)	0.97	0.60-1.57	-0.024 (0.297)	0.98	0.54-1.77
Lozenge vs. sublingual (0)		0.240 (0.292)	1.27	0.71-2.28	0.250 (0.353)	1.28	0.63-2.60
P(placebo is best)	0.0						
P(patch is best)	0.8						
P(gum is best)	0.6						
P(inhaler is best)	24.8						
P(spray is best)	34.8						
P(sublingual is best)	9.1						

<b>Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations</b>							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(lozenge is best)	29.9						
Placebo rate (SE): 0.094 (0.010)							
<b>CAR at 2 y</b>							
Gum vs. placebo (2)		0.856 (0.280)	2.35	1.34-4.12	0.971 (0.702)	2.64	0.65-10.75
Patch vs. placebo (2)		1.376 (0.340)	3.96	2.01-7.81	1.558 (0.811)	4.75	0.94-24.04
Inhaler vs. placebo (1)		1.401 (1.123)	4.06	0.43-38.34	1.804 (1.663)	6.07	0.22-169.05
Spray vs. placebo (1)		0.356 (0.434)	1.43	0.60-3.40	0.352 (1.017)	1.42	0.19-10.87
Patch vs. gum (0)		0.520 (0.440)	1.68	0.70-4.06	0.587 (1.092)	1.80	0.20-15.98
Inhaler vs. gum (0)		0.545 (1.157)	1.73	0.17-17.45	0.834 (1.822)	2.30	0.06-88.00
Spray vs. gum (0)		-0.500 (0.516)	0.61	0.22-1.70	-0.619 (1.237)	0.54	0.05-6.39
Inhaler vs. patch (0)		0.026 (1.173)	1.03	0.10-10.71	0.246 (1.886)	1.28	0.03-55.61
Spray vs. patch (0)		-1.020 (0.551)	0.36	0.12-1.09	-1.206 (1.234)	0.30	0.03-3.53
Spray vs. inhaler (0)		-1.046 (1.203)	0.35	0.03-3.90	-1.452 (1.986)	0.23	0.00-12.43
P(placebo is best)	0.1						
P(gum is best)	11.2						
P(patch is best)	35.6						
P(inhaler is best)	49.3						
P(spray is best)	3.8						
Placebo rate (SE): 0.055 (0.031)							
<b>CAR at 3 y</b>							
Patch vs. placebo (2)		1.191 (0.345)	3.29	1.65-6.56	1.258 (0.706)	3.52	0.86-14.43
P(placebo is best)	3.1						
P(patch is best)	96.9						
Placebo rate (SE): 0.046 (0.039)							
<b>CAR at 4 y</b>							
Gum vs. placebo (1)		0.002 (0.266)	1.00	0.59-1.71	-0.008 (0.261)	0.99	0.59-1.67
P(placebo is best)	50.9						
P(gum is best)	49.1						
Placebo rate (SE): none							

<b>Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations</b>							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b><i>CAR at 5 y</i></b>							
Patch vs. placebo (2)		0.574 (0.302)	1.78	0.97-3.25	0.543 (0.731)	1.72	0.40-7.43
P(placebo is best)	17.1						
P(patch is best)	82.9						
Placebo rate (SE): 0.099 (0.090)							
<b><i>CAR at 7 y</i></b>							
Patch vs. placebo (1)		1.478 (0.571)	4.38	1.40-13.74	1.424 (0.588)	4.15	1.28-13.45
P(placebo is best)	0.5						
P(patch is best)	99.5						
Placebo rate (SE): none							
<b><i>CAR at 8 y</i></b>							
Patch vs. placebo (1)		0.326 (0.228)	1.39	0.88-2.19	0.317 (0.230)	1.37	0.87-2.18
P(placebo is best)	8.7						
P(patch is best)	91.3						
Placebo rate (SE): none							
<b><i>CAR at 10 y</i></b>							
Patch vs. placebo (1)		1.161 (0.589)	3.19	0.98-10.37	1.090 (0.577)	2.97	0.94-9.43
P(placebo is best)							
P(patch is best)	2.5						
Placebo rate (SE): none	97.5						
<b><i>PAR at 6 m</i></b>							
Spray vs. placebo (1)		0.794 (0.276)	2.21	1.27-3.84	0.831 (1.211)	2.29	0.20-25.84
Patch vs. placebo (0)		0.997 (0.381)	2.71	1.27-5.81	1.031 (1.690)	2.80	0.10-82.42
Patch vs. spray (1)		0.203 (0.470)	1.23	0.48-3.14	0.201 (1.209)	1.22	0.11-13.70
P(placebo is best)	11.3						
P(spray is best)	31.9						
P(patch is best)	56.8						
Placebo rate (SE): none							

**Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>PAR at 1 y</b>							
Spray vs. placebo (2)		0.776 (0.231)	2.17	1.37-3.45	0.822 (0.696)	2.27	0.56-9.16
Gum vs. placebo (1)		1.202 (0.452)	3.33	1.35-8.22	1.259 (1.024)	3.52	0.45-27.31
Patch vs. placebo (1)		0.909 (0.320)	2.48	1.31-4.71	0.891 (0.952)	2.44	0.36-16.37
Gum vs. spray (0)		0.426 (0.508)	1.53	0.55-4.23	0.438 (1.209)	1.55	0.14-17.40
Patch vs. spray (0)		0.133 (0.395)	1.14	0.52-2.52	0.069 (1.192)	1.07	0.10-11.62
Patch vs. gum (0)		-0.293 (0.554)	0.75	0.25-2.26	-0.369 (1.376)	0.69	0.04-10.84
P(placebo is best)	0.3						
P(spray is best)	18.8						
P(gum is best)	52.2						
P(patch is best)	28.7						
Placebo rate (SE): 0.140 (0.033)							
<b>PPA at 6 m</b>							
Gum vs. placebo (9)		0.502 (0.104)	1.65	1.34-2.03	0.518 (0.126)	1.68	1.31-2.16
Patch vs. placebo (6)		0.594 (0.120)	1.81	1.43-2.30	0.622 (0.151)	1.86	1.38-2.52
Inhaler vs. placebo (1)		0.979 (0.287)	2.66	1.50-4.73	0.989 (0.328)	2.69	1.39-5.18
Spray vs. placebo (0)		0.429 (0.213)	1.54	1.00-2.35	0.451 (0.252)	1.57	0.95-2.60
Lozenge vs. placebo (0)		0.713 (0.350)	2.04	1.01-4.11	0.741 (0.402)	2.10	0.94-4.69
Patch vs. gum (0)		0.092 (0.158)	1.10	0.80-1.51	0.104 (0.193)	1.11	0.75-1.63
Inhaler vs. gum (1)		0.477 (0.305)	1.61	0.88-2.97	0.470 (0.353)	1.60	0.79-3.24
Spray vs. gum (1)		-0.073 (0.236)	0.93	0.58-1.49	-0.068 (0.272)	0.93	0.54-1.61
Lozenge vs. gum (1)		0.212 (0.365)	1.24	0.60-2.56	0.223 (0.381)	1.25	0.58-2.68
Inhaler vs. patch (0)		0.385 (0.311)	1.47	0.79-2.74	0.366 (0.349)	1.44	0.72-2.90
Spray vs. patch (2)		-0.165 (0.244)	0.85	0.52-1.38	-0.171 (0.217)	0.84	0.55-1.30
Lozenge vs. patch (0)		0.119 (0.370)	1.13	0.54-2.36	0.119 (0.427)	1.13	0.48-2.64
Spray vs. inhaler (1)		-0.550 (0.357)	0.58	0.28-1.18	-0.538 (0.374)	0.58	0.28-1.23
Lozenge vs. inhaler (0)		-0.266 (0.453)	0.77	0.31-1.90	-0.248 (0.539)	0.78	0.27-2.29
Lozenge vs. spray (0)		0.284 (0.410)	1.33	0.59-3.02	0.290 (0.462)	1.34	0.53-3.37
P(placebo is best)	0.0						

<b>Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations</b>							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(gum is best)	0.9						
P(patch is best)	5.6						
P(inhaler is best)	62.3						
P(spray is best)	1.7						
P(lozenge is best)	29.5						
Placebo rate (SE): 0.189 (0.034)							
<b>PPA at 1 y</b>							
Gum vs. placebo (9)		0.730 (0.123)	2.07	1.62-2.65	0.732 (0.170)	2.08	1.48-2.92
Patch vs. placebo (5)		0.543 (0.128)	1.72	1.33-2.22	0.562 (0.195)	1.75	1.19-2.59
Inhaler vs. placebo (3)		0.899 (0.244)	2.46	1.51-4.01	0.929 (0.311)	2.53	1.36-4.71
Lozenge vs. placebo (0)		1.051 (0.387)	2.86	1.32-6.20	1.066 (0.531)	2.90	1.00-8.40
Patch vs. gum (0)		-0.186 (0.178)	0.83	0.58-1.18	-0.170 (0.256)	0.84	0.51-1.41
Inhaler vs. vs. gum (0)		0.170 (0.274)	1.18	0.69-2.05	0.196 (0.351)	1.22	0.60-2.45
Lozenge vs. gum (1)		0.321 (0.406)	1.38	0.61-3.11	0.333 (0.498)	1.40	0.52-3.78
Inhaler vs. patch (0)		0.356 (0.276)	1.43	0.82-2.48	0.366 (0.360)	1.44	0.70-2.96
Lozenge vs. patch (0)		0.508 (0.408)	1.66	0.74-3.76	0.503 (0.567)	1.65	0.53-5.14
Lozenge vs. inhaler (0)		0.152 (0.458)	1.16	0.47-2.91	0.137 (0.626)	1.15	0.33-4.01
P(placebo is best)	0.0						
P(gum is best)	5.2						
P(patch is best)	2.6						
P(inhaler is best)	36.0						
P(lozenge is best)	56.2						
Placebo rate (SE): 0.118 (0.023)							
<b>PPA at 15 m</b>							
Inhaler vs. placebo (1)		1.798 (0.634)	6.04	1.70-21.46	1.727 (0.621)	5.62	1.62-19.47
P(placebo is best)	0.1						
P(inhaler is best)	99.9						
Placebo rate (SE): none							

Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>PPA at 2 y</b>							
Gum vs. placebo (2)		0.740 (0.252)	2.10	1.27-3.47	0.794 (0.726)	2.21	0.52-9.45
Inhaler vs. placebo (1)		0.233 (0.343)	1.26	0.64-2.51	0.291 (1.020)	1.34	0.17-10.28
Inhaler vs. gum (0)		-0.506 (0.426)	0.60	0.26-1.41	-0.503 (1.207)	0.60	0.05-6.76
P(placebo is best)	3.6						
P(gum is best)	72.1						
P(inhaler is best)	24.3						
Placebo rate (SE):0.123 (0.091)							
<b>Relapse at 1 y<sup>s</sup></b>							
Patch vs. placebo (11)		0.802 (0.089)	2.23	1.87-2.66	0.833 (0.113)	2.30	1.83-2.89
Gum vs. placebo (5)		0.645 (0.163)	1.91	1.38-2.64	0.667 (0.186)	1.95	1.34-2.83
Spray vs. placebo (4)		1.113 (0.248)	3.04	1.85-5.00	1.120 (0.268)	3.07	1.80-5.24
Inhaler vs. placebo (3)		0.799 (0.332)	2.22	1.14-4.32	0.807 (0.354)	2.24	1.10-4.54
Sublingual vs. placebo (2)		1.004 (0.305)	2.73	1.48-5.02	1.004 (0.324)	2.73	1.43-5.22
Lozenge vs. placebo (1)		0.724 (0.140)	2.06	1.56-2.73	0.741 (0.216)	2.10	1.36-3.23
Gum vs. patch (0)		-0.157 (0.186)	0.85	0.59-1.24	-0.166 (0.211)	0.85	0.55-1.29
Spray vs. patch (0)		0.311 (0.264)	1.36	0.81-2.31	0.287 (0.285)	1.33	0.75-2.35
Inhaler vs. patch (0)		-0.003 (0.344)	1.00	0.50-1.98	-0.027 (0.376)	0.97	0.46-2.06
Sublingual vs. patch (0)		0.201 (0.317)	1.22	0.65-2.31	0.171 (0.337)	1.19	0.60-2.33
Lozenge vs. patch (0)		-0.078 (0.166)	0.93	0.66-1.29	-0.092 (0.243)	0.91	0.56-1.48
Spray vs. gum (0)		0.468 (0.297)	1.60	0.88-2.89	0.454 (0.329)	1.57	0.82-3.04
Inhaler vs. gum (0)		0.153 (0.370)	1.17	0.56-2.44	0.140 (0.400)	1.15	0.52-2.56
Sublingual vs. gum (0)		0.358 (0.345)	1.43	0.72-2.86	0.337 (0.364)	1.40	0.68-2.90
Lozenge vs. gum (0)		0.079 (0.215)	1.08	0.70-1.66	0.074 (0.296)	1.08	0.60-1.95
Inhaler vs. spray (0)		-0.314 (0.415)	0.73	0.32-1.67	-0.314 (0.433)	0.73	0.31-1.74
Sublingual vs. spray (0)		-0.109 (0.393)	0.90	0.41-1.97	-0.116 (0.428)	0.89	0.38-2.09
Lozenge vs. spray (0)		-0.389 (0.285)	0.68	0.38-1.20	-0.379 (0.346)	0.68	0.34-1.37
Sublingual vs. inhaler (0)		0.205 (0.451)	1.23	0.50-3.02	0.197 (0.491)	1.22	0.46-3.25
Lozenge vs. inhaler (0)		-0.074 (0.361)	0.93	0.45-1.91	-0.066 (0.420)	0.94	0.40-2.17

<b>Appendix 8c: Comparison between NRTs for smoking cessation in relatively healthy and motivated-to-quit populations</b>							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Lozenge vs. sublingual(0)		-0.279 (0.335)	0.76	0.39-1.48	-0.263 (0.395)	0.77	0.35-1.69
P(placebo is worst)	0.00						
P(patch is worst)	1.9						
P(gum is worst)	1.5						
P(spray is worst)	46.6						
P(inhaler is worst)	14.7						
P(sublingual is worst)	31.1						
P(lozenge is worst)	4.2						
Placebo rate (SE): 0.058 (0.008)							

§ relapse = proportion of quitters at 3 months was detected as smokers at 1 year

CAR: continuous abstinence rate; CI: confidence interval; CrI: credible interval; m: month; OR: odds ratio; P: probability; PAR: prolonged abstinence rate; PPA: point prevalence abstinence; SE: standard error; y: year

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>Any adverse events</b>							
Bupropion vs. placebo (11)		0.525 (0.061)	1.69	1.50-1.91	0.542 (0.105)	1.72	1.39-2.12
Patch vs. placebo (6)		0.396 (0.090)	1.49	1.24-1.78	0.410 (0.142)	1.51	1.13-2.00
Varenicline vs. placebo (8)		0.602 (0.079)	1.82	1.56-2.14	0.603 (0.119)	1.83	1.44-2.32
Gum vs. placebo (2)		0.466 (0.066)	1.59	1.40-1.82	0.454 (0.188)	1.58	1.08-2.30
Inhaler vs. placebo (2)		0.111 (0.147)	1.12	0.83-1.50	0.119 (0.235)	1.13	0.70-1.80
Sublingual vs. placebo (2)		0.790 (0.271)	2.20	1.28-3.79	0.840 (0.358)	2.32	1.13-4.74
Lozenge vs. placebo (1)		0.690 (0.092)	1.99	1.66-2.40	0.743 (0.232)	2.10	1.32-3.34
Spray vs. placebo (0)		1.662 (0.578)	5.27	1.66-16.74	1.753 (0.650)	5.77	1.57-21.18
Patch vs. bupropion (0)		-0.129 (0.108)	0.88	0.71-1.09	-0.131 (0.176)	0.88	0.62-1.25
Varenicline vs. bupropion (2)		0.076 (0.100)	1.08	0.88-1.32	0.061 (0.148)	1.06	0.79-1.43
Gum vs. bupropion (0)		-0.059 (0.090)	0.94	0.79-1.13	-0.087 (0.217)	0.92	0.59-1.42
Inhaler vs. bupropion (0)		-0.415 (0.159)	0.66	0.48-0.91	-0.423 (0.257)	0.66	0.39-1.10
Sublingual vs. bupropion (0)		0.265 (0.277)	1.30	0.75-2.27	0.298 (0.371)	1.35	0.64-2.83
Lozenge vs. bupropion (0)		0.164 (0.110)	1.18	0.95-1.47	0.201 (0.253)	1.22	0.74-2.03
Spray vs. bupropion (0)		1.137 (0.581)	3.12	0.98-9.96	1.211 (0.656)	3.36	0.90-12.46
Varenicline vs. patch (1)		0.205 (0.120)	1.23	0.97-1.56	0.192 (0.179)	1.21	0.85-1.73
Gum vs. patch (0)		0.070 (0.111)	1.07	0.86-1.34	0.044 (0.232)	1.04	0.66-1.66
Inhaler vs. patch (0)		-0.286 (0.172)	0.75	0.53-1.06	-0.291 (0.273)	0.75	0.43-1.29
Sublingual vs. patch		0.394 (0.285)	1.48	0.84-2.62	0.430 (0.382)	1.54	0.72-3.30
Lozenge vs. patch (0)		0.293 (0.129)	1.34	1.04-1.73	0.333 (0.272)	1.39	0.81-2.40
Spray vs. patch (1)		1.266 (0.585)	3.55	1.10-11.42	1.342 (0.640)	3.83	1.07-13.76
Gum vs. varenicline (0)		-0.135 (0.103)	0.87	0.71-1.07	-0.148 (0.224)	0.86	0.55-1.35
Inhaler vs. varenicline (0)		-0.491 (0.167)	0.61	0.44-0.85	-0.484 (0.263)	0.62	0.36-1.04
Sublingual vs. varenicline (0)		0.189 (0.282)	1.21	0.69-2.12	0.237 (0.376)	1.27	0.60-2.69
Lozenge vs. varenicline (0)		0.088 (0.121)	1.09	0.86-1.39	0.140 (0.257)	1.15	0.69-1.92
Spray vs. varenicline (0)		1.061 (0.583)	2.89	0.90-9.27	1.150 (0.657)	3.16	0.85-11.76
Inhaler vs. gum (0)		-0.355 (0.161)	0.70	0.51-0.97	-0.335 (0.306)	0.72	0.39-1.32
Sublingual vs. gum (0)		0.324 (0.278)	1.38	0.79-2.41	0.386 (0.396)	1.47	0.67-3.25

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Lozenge vs. gum (1)		0.223 (0.113)	1.25	1.00-1.57	0.289 (0.260)	1.33	0.79-2.25
Spray vs. gum (0)		1.196 (0.582)	3.31	1.03-10.58	1.298 (0.680)	3.66	0.94-14.26
Sublingual vs. inhaler (0)		0.679 (0.308)	1.97	1.07-3.65	0.721 (0.432)	2.06	0.87-4.88
Lozenge vs. inhaler (0)		0.579 (0.173)	1.78	1.26-2.52	0.624 (0.336)	1.87	0.95-3.66
Spray vs. inhaler (0)		1.552 (0.596)	4.72	1.43-15.55	1.634 (0.693)	5.12	1.28-20.48
Lozenge vs. sublingual (0)		-0.100 (0.286)	0.90	0.51-1.60	-0.097 (0.424)	0.91	0.39-2.12
Spray vs. sublingual (0)		0.872 (0.638)	2.39	0.67-8.57	0.913 (0.737)	2.49	0.57-10.87
Spray vs. lozenge (0)		0.973 (0.585)	2.64	0.82-8.52	1.010 (0.678)	2.74	0.71-10.66
P(placebo is worst)	0.0						
P(bupropion is worst)	0.0						
P(patch is worst)	0.0						
P(varenicline is worst)	0.6						
P(gum is worst)	0.0						
P(inhaler is worst)	0.1						
P(sublingual is worst)	8.6						
P(lozenge is worst)	3.3						
P(spray is worst)	87.4						
Placebo rate (SE): 0.575 (0.049)							
Discontinued due to adverse events							
Patch vs. placebo (12)		0.439 (0.105)	1.55	1.26-1.91	0.341 (0.160)	1.41	1.02-1.94
Bupropion vs. placebo (14)		0.577 (0.095)	1.78	1.47-2.15	0.554 (0.142)	1.74	1.31-2.31
Varenicline vs. placebo (9)		0.386 (0.109)	1.47	1.18-1.83	0.419 (0.166)	1.52	1.09-2.12
Inhaler vs. placebo (2)		0.236 (0.401)	1.27	0.57-2.82	0.294 (0.487)	1.34	0.51-3.56
Gum vs. placebo (1)		16.12 (1.6e+3)	10e+6	0.0-∞	38.62 (29.52)	6e+16	0.0-∞
Lozenge vs. placebo (1)		0.0 (0.183)	1.00	0.69-1.44	-0.009 (0.410)	0.99	0.44-2.25
Bupropion vs. patch (2)		0.138 (0.141)	1.15	0.86-1.52	0.213 (0.195)	1.24	0.84-1.83
Varenicline vs. patch (1)		-0.053 (0.152)	0.95	0.70-1.28	0.078 (0.212)	1.08	0.71-1.65
Inhaler vs. patch (0)		-0.204 (0.415)	0.82	0.36-1.87	-0.047 (0.524)	0.95	0.33-2.72
Gum vs. patch (0)		15.68 (1.6e+3)	6e+6	0.0-∞	38.28 (29.52)	4e+16	0.0-∞

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Lozenge vs. patch (0)		-0.439 (0.211)	0.64	0.42-0.98	-0.351 (0.439)	0.70	0.29-1.70
Varenicline vs. bupropion (3)		-0.019 (0.145)	0.83	0.62-1.10	-0.135 (0.193)	0.87	0.59-1.28
Inhaler vs. bupropion (0)		-0.341 (0.412)	0.71	0.31-1.62	-0.260 (0.504)	0.77	0.28-2.11
Gum vs. bupropion (0)		1.55 (1.6e+3)	6e+6	0.0-∞	38.06 (29.52)	3e+16	0.0-∞
Lozenge vs. bupropion (0)		-0.577 (0.206)	0.56	0.37-0.85	-0.564 (0.433)	0.57	0.24-1.35
Inhaler vs. varenicline (0)		-0.150 (0.416)	0.86	0.37-1.98	-0.125 (0.508)	0.88	0.32-2.44
Gum vs. varenicline (0)		15.73 (1.6e+3)	7e+6	0.0-∞	38.20 (29.52)	4e+16	0.0-∞
Lozenge vs. varenicline (0)		-0.386 (0.213)	0.68	0.44-1.04	-0.428 (0.441)	0.65	0.27-1.57
Gum vs. inhaler (0)		15.88 (1.6e+3)	8e+6	0.0-∞	38.32 (29.51)	4e+16	0.0-∞
Lozenge vs. inhaler (0)		-0.236 (0.441)	0.79	0.33-1.91	-0.304 (0.629)	0.74	0.21-2.60
Lozenge vs. gum (0)		-16.11 (1.6e+3)	0.0	0.0-∞	-38.63 (29.52)	0.0	0.0-∞
P(placebo is worst)	0.0						
P(patch is worst)	0.1						
P(bupropion is worst)	0.3						
P(varenicline is worst)	0.0						
P(inhaler is worst)	0.0						
P(gum is worst)	99.6						
P(lozenge is worst)	0.0						
Placebo rate (SE): 0.041 (0.006)							
Nonfatal serious adverse events							
Bupropion vs. placebo (11)		0.906 (0.292)	2.48	1.38-4.44	1.001 (0.391)	2.72	1.24-5.96
Varenicline vs. placebo (6)		-0.065 (0.302)	0.94	0.51-1.72	-0.216 (0.446)	0.81	0.33-1.97
Inhaler vs. placebo (3)		0.054 (0.368)	1.06	0.51-2.20	0.119 (0.639)	1.13	0.31-4.04
Patch vs. placebo (3)		0.709 (0.545)	2.03	0.68-6.05	0.561 (0.735)	1.75	0.40-7.62
Lozenge vs. placebo (1)		0.980 (0.418)	2.66	1.15-6.15	0.991 (0.805)	2.70	0.54-13.49
Varenicline vs. bupropion (2)		-0.971 (0.420)	0.38	0.16-0.88	-1.217 (0.544)	0.30	0.10-0.88
Inhaler vs. bupropion (0)		-0.852 (0.469)	0.43	0.17-1.09	-0.883 (0.749)	0.41	0.09-1.85
Patch vs. bupropion (1)		-0.197 (0.618)	0.82	0.24-2.83	-0.440 (0.774)	0.64	0.14-3.03
Lozenge vs. bupropion (0)		0.073 (0.510)	1.08	0.39-2.98	-0.010 (0.902)	0.99	0.16-6.02

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Inhaler vs. varenicline (0)		0.119 (0.476)	1.13	0.43-2.92	0.335 (0.789)	1.40	0.29-6.77
Patch vs. varenicline (1)		0.774 (0.623)	2.17	0.62-7.55	0.777 (0.723)	2.18	0.51-9.23
Lozenge vs. varenicline (0)		1.044 (0.516)	2.84	1.01-7.98	1.207 (0.937)	3.34	0.51-21.80
Patch vs. inhaler (0)		0.655 (0.657)	1.93	0.52-7.17	0.442 (0.958)	1.56	0.23-10.58
Lozenge vs. inhaler (0)		0.926 (0.557)	2.52	0.83-7.68	0.873 (1.023)	2.39	0.31-18.52
Lozenge vs. patch (0)		0.270 (0.687)	1.31	0.33-5.18	0.430 (1.111)	1.54	0.17-14.19
P(placebo is worst)	0.0						
P(bupropion is worst)	35.1						
P(varenicline is worst)	0.1						
P(inhaler is worst)	5.1						
P(patch is worst)	17.3						
P(lozenge is worst)	42.4						
Placebo rate (SE): 0.010 (0.002)							
<b>Hospitalized</b>							
Bupropion vs. placebo (2)		0.003 (0.582)	1.00	0.31-3.21	-0.371 (1.190)	0.69	0.06-7.44
P(placebo is worst)	61.3						
P(bupropion is worst)	38.7						
Placebo rate (SE): 0.018 (0.029)							
<b>Influenza</b>							
Varenicline vs. placebo (3)		0.156 (0.287)	1.17	0.66-2.08	0.237 (0.538)	1.27	0.43-3.72
Bupropion vs. placebo (2)		-0.329 (0.257)	0.72	0.43-1.20	-0.304 (0.514)	0.74	0.26-2.06
Patch vs. placebo (1)		-0.453 (0.329)	0.64	0.33-1.23	-0.437 (0.721)	0.65	0.15-2.74
Bupropion vs. varenicline		-0.485 (0.386)	0.62	0.28-1.33	-0.541 (0.707)	0.58	0.14-2.39
Patch vs. varenicline (0)		-0.609 (0.437)	0.54	0.23-1.30	-0.674 (0.882)	0.51	0.09-2.98
Patch vs. bupropion (1)		-0.124 (0.418)	0.88	0.38-2.04	-0.132 (0.738)	0.88	0.20-3.83
P(placebo is worst)	19.8						
P(varenicline is worst)	61.0						
P(bupropion is worst)	8.8						
P(patch is worst)	10.4						

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Placebo rate (SE): 0.059 (0.023)							
<b>Respiratory tract infection</b>							
Varenicline vs. placebo (6)		0.117 (0.110)	1.12	0.90-1.40	0.141 (0.164)	1.15	0.83-1.60
Bupropion vs. placebo (6)		-0.198 (0.120)	0.82	0.65-1.04	-0.211 (0.171)	0.81	0.58-1.14
Lozenge vs. placebo (1)		0.321 (0.161)	1.38	1.00-1.90	0.308 (0.338)	1.36	0.69-2.67
Patch vs. placebo (2)		-0.196 (0.253)	0.82	0.50-1.36	-0.227 (0.349)	0.80	0.40-1.60
Sublingual vs. placebo (1)		-0.405 (0.922)	0.67	0.11-4.22	-0.489 (1.069)	0.61	0.07-5.20
Bupropion vs. varenicline (2)		-0.315 (0.163)	0.73	0.53-1.01	-0.351 (0.210)	0.70	0.46-1.07
Lozenge vs. varenicline (0)		0.204 (0.196)	1.23	0.83-1.81	0.167 (0.376)	1.18	0.56-2.51
Patch vs. varenicline (0)		-0.313 (0.276)	0.73	0.42-1.27	-0.367 (0.388)	0.69	0.32-1.50
Sublingual vs. varenicline (0)		-0.523 (0.929)	0.59	0.09-3.80	-0.629 (1.080)	0.53	0.06-4.62
Lozenge vs. bupropion (0)		0.519 (0.201)	1.68	1.12-2.51	0.518 (0.384)	1.68	0.78-3.62
Patch vs. bupropion (1)		0.002 (0.280)	1.00	0.57-1.75	-0.016 (0.350)	0.98	0.49-1.98
Sublingual vs. bupropion (0)		-0.208 (0.930)	0.81	0.13-5.22	-0.278 (1.086)	0.76	0.09-6.65
Patch vs. lozenge (0)		-0.517 (0.300)	0.60	0.33-1.09	-0.534 (0.477)	0.59	0.23-1.52
Sublingual vs. lozenge (0)		-0.727 (0.936)	0.48	0.07-3.14	-0.796 (1.120)	0.45	0.05-4.24
Sublingual vs. patch (0)		-0.210 (0.956)	0.81	0.12-5.49	-0.262 (1.130)	0.77	0.08-7.37
P(placebo is worst)	1.1						
P(varenicline is worst)	17.4						
P(bupropion is worst)	0.5						
P(lozenge is worst)	54.6						
P(patch is worst)	5.2						
P(sublingual is worst)	21.2						
Placebo rate (SE): 0.103 (0.028)							
<b>Headache</b>							
Bupropion vs. placebo (17)		0.046 (0.069)	1.05	0.91-1.20	0.065 (0.095)	1.07	0.88-1.29
Patch vs. placebo (12)		0.015 (0.074)	1.02	0.87-1.18	0.005 (0.103)	1.01	0.82-1.24
Gum vs. placebo (4)		-0.194 (0.167)	0.82	0.59-1.15	-0.191 (0.200)	0.83	0.55-1.23
Varenicline vs. placebo (7)		0.321 (0.088)	1.38	1.16-1.64	0.341 (0.119)	1.41	1.11-1.79

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Spray vs. placebo (3)		0.294 (0.170)	1.34	0.96-1.89	0.299 (0.213)	1.35	0.88-2.07
Lozenge vs. placebo (1)		0.360 (0.208)	1.43	0.95-2.17	0.362 (0.312)	1.44	0.77-2.68
Patch vs. bupropion (2)		-0.031 (0.102)	0.97	0.79-1.19	-0.060 (0.129)	0.94	0.73-1.22
Gum vs. bupropion (0)		-0.240 (0.181)	0.79	0.55-1.13	-0.256 (0.224)	0.77	0.49-1.21
Varenicline vs. bupropion (3)		0.274 (0.112)	1.32	1.05-1.65	0.276 (0.134)	1.32	1.01-1.72
Spray vs. bupropion (0)		0.248 (0.184)	1.28	0.89-1.85	0.234 (0.232)	1.26	0.79-2.01
Lozenge vs. bupropion (0)		0.313 (0.219)	1.37	0.88-2.12	0.297 (0.334)	1.35	0.69-2.62
Gum vs. patch (0)		-0.209 (0.183)	0.81	0.56-1.17	-0.196 (0.225)	0.82	0.52-1.29
Varenicline vs. patch (1)		0.305 (0.115)	1.36	1.08-1.71	0.335 (0.147)	1.40	1.04-1.88
Spray vs. patch (0)		0.279 (0.186)	1.32	0.91-1.92	0.293 (0.239)	1.34	0.83-2.16
Lozenge vs. patch (0)		0.34 (0.221)	1.41	0.91-2.19	0.357 (0.335)	1.43	0.73-2.79
Varenicline vs. gum (0)		0.514 (0.189)	1.67	1.15-2.44	0.532 (0.229)	1.70	1.08-2.69
Spray vs. gum (0)		0.488 (0.238)	1.63	1.01-2.62	0.490 (0.297)	1.63	0.90-2.95
Lozenge vs. gum		0.553 (0.266)	1.74	1.02-2.96	0.553 (0.373)	1.74	0.82-3.67
Spray vs. varenicline		-0.026 (0.191)	0.97	0.66-1.43	-0.042 (0.244)	0.96	0.59-1.56
Lozenge vs. varenicline		0.039 (0.225)	1.04	0.66-1.63	0.021 (0.335)	1.02	0.52-2.00
Lozenge vs. spray		0.065 (0.268)	1.07	0.62-1.83	0.063 (0.384)	1.07	0.49-2.30
P(placebo is worst)	0.0						
P(bupropion is worst)	0.1						
P(patch is worst)	0.0						
P(gum is worst)	0.2						
P(varenicline is worst)	28.1						
P(spray is worst)	28.3						
P(lozenge is worst)	43.3						
Placebo rate (SE): 0.111 (0.017)							
<b>Dizziness</b>							
Bupropion vs. placebo (10)		0.232 (0.119)	1.26	0.99-1.60	0.242 (0.133)	1.27	0.8-1.66
Patch vs. placebo (5)		-0.423 (0.223)	0.65	0.42-1.02	-0.379 (0.262)	0.68	0.41-1.16
Spray vs. placebo (3)		0.197 (0.182)	1.22	0.85-1.75	0.203 (0.223)	1.22	0.78-1.91

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Gum vs. placebo (2)		0.424 (0.502)	1.53	0.56-4.17	0.473 (0.568)	1.61	0.52-5.00
Varenicline vs. placebo (4)		0.212 (0.152)	1.24	0.91-1.67	0.231 (0.182)	1.26	0.88-1.81
Patch vs. bupropion (1)		-0.655 (0.253)	0.52	0.31-0.86	-0.621 (0.267)	0.54	0.32-0.92
Spray vs. bupropion (0)		-0.035 (0.217)	0.97	0.63-1.49	-0.039 (0.258)	0.96	0.57-1.61
Gum vs. bupropion (0)		0.192 (0.516)	1.21	0.43-3.40	0.231 (0.586)	1.26	0.39-4.07
Varenicline vs. bupropion (2)		-0.020 (0.192)	0.98	0.67-1.44	-0.011 (0.196)	0.99	0.67-1.47
Spray vs. patch (0)		0.620 (0.288)	1.86	1.05-3.31	0.582 (0.344)	1.79	0.90-3.56
Gum vs. patch (0)		0.847 (0.549)	2.33	0.78-7.00	0.852 (0.622)	2.35	0.68-8.13
Varenicline vs. patch (1)		0.635 (0.270)	1.89	1.10-3.24	0.611 (0.265)	1.84	1.08-3.13
Gum vs. spray (0)		0.227 (0.534)	1.25	0.43-3.65	0.270 (0.619)	1.31	0.38-4.52
Varenicline vs. spray (0)		0.015 (0.237)	1.01	0.63-1.63	0.028 (0.289)	1.03	0.58-1.84
Varenicline vs. gum (0)		-0.212 (0.524)	0.81	0.28-2.31	-0.242 (0.598)	0.79	0.24-2.60
P(placebo is worst)	0.0						
P(bupropion is worst)	12.8						
P(patch is worst)	0.1						
P(spray is worst)	15.5						
P(gum is worst)	57.6						
P(varenicline is worst)	14.0						
Placebo rate (SE): 0.058 (0.018)							
<b>Gastritis</b>							
Sublingual vs. placebo (1)		0.927 (0.506)	2.53	0.92-6.95	0.892 (0.506)	2.44	0.89-6.72
P(placebo is worst)	3.2						
P(sublingual is worst)	96.8						
Placebo rate (SE): none							
<b>Nausea/vomiting</b>							
Patch vs. placebo (13)		0.145 (0.093)	1.16	0.96-1.39	0.213 (0.143)	1.24	0.93-1.65
Bupropion vs. placebo (11)		0.387 (0.097)	1.47	1.21-1.79	0.420 (0.145)	1.52	1.14-2.03
Varenicline vs. placebo (9)		1.476 (0.084)	4.37	3.70-5.17	1.423 (0.139)	4.15	3.14-5.48
Gum vs. placebo (5)		0.464 (0.171)	1.59	1.13-2.24	0.467 (0.247)	1.60	0.97-2.62

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Inhaler vs. placebo (3)		0.285 (0.271)	1.33	0.77-2.29	0.296 (0.348)	1.34	0.67-2.70
Spray vs. placebo (3)		0.594 (0.222)	1.81	1.16-2.82	0.628 (0.308)	1.87	1.01-3.47
Sublingual vs. placebo (2)		1.484 (0.343)	4.41	2.22-8.75	1.549 (0.426)	4.71	2.01-11.03
Lozenge vs. placebo (1)		1.062 (0.169)	2.89	2.06-4.05	1.066 (0.337)	2.90	1.48-5.70
Bupropion vs. patch (2)		0.242 (0.134)	1.27	0.97-1.67	0.207 (0.184)	1.23	0.85-1.78
Varenicline vs. patch (1)		1.330 (0.125)	3.78	2.95-4.85	1.210 (0.180)	3.36	2.34-4.81
Gum vs. patch (0)		0.319 (0.194)	1.38	0.93-2.03	0.255 (0.283)	1.29	0.73-2.27
Inhaler vs. patch (0)		0.139 (0.286)	1.15	0.65-2.04	0.083 (0.379)	1.09	0.51-2.32
Spray vs. patch (0)		0.449 (0.240)	1.57	0.97-2.53	0.415 (0.336)	1.52	0.77-2.96
Sublingual vs. patch (0)		1.338 (0.355)	3.81	1.88-7.75	1.336 (0.448)	3.80	1.55-9.32
Lozenge vs. patch (0)		0.917 (0.192)	2.50	1.70-3.67	0.854 (0.356)	2.35	1.15-4.79
Varenicline vs. bupropion (3)		1.088 (0.128)	2.97	2.30-3.84	1.004 (0.171)	2.73	1.94-3.84
Gum vs. bupropion (0)		0.077 (0.197)	1.08	0.73-1.60	0.048 (0.288)	1.05	0.59-1.87
Inhaler vs. bupropion (0)		-0.103 (0.288)	0.90	0.51-1.60	-0.123 (0.380)	0.88	0.41-1.89
Spray vs. bupropion (0)		0.207 (0.242)	1.23	0.76-1.99	0.209 (0.343)	1.23	0.62-2.44
Sublingual vs. bupropion (0)		1.096 (0.356)	2.99	1.47-6.10	1.129 (0.457)	3.09	1.24-7.72
Lozenge vs. bupropion (0)		0.675 (0.195)	1.96	1.33-2.90	0.647 (0.371)	1.91	0.91-4.01
Gum vs. varenicline (0)		-1.011 (0.190)	0.36	0.25-0.53	-0.956 (0.288)	0.38	0.22-0.68
Inhaler vs. varenicline (0)		-1.191 (0.284)	0.30	0.17-0.54	-1.127 (0.375)	0.32	0.15-0.69
Spray vs. varenicline (0)		-0.882 (0.237)	0.41	0.26-0.66	-0.795 (0.346)	0.45	0.23-0.90
Sublingual vs. varenicline (0)		0.008 (0.353)	1.01	0.50-2.04	0.126 (0.457)	1.13	0.45-2.83
Lozenge vs. varenicline (0)		-0.414 (0.188)	0.66	0.45-0.96	-0.357 (0.359)	0.70	0.34-1.44
Inhaler vs. gum (0)		-0.180 (0.320)	0.84	0.44-1.59	-0.171 (0.444)	0.84	0.35-2.05
Spray vs. gum (0)		0.130 (0.280)	1.14	0.65-1.99	0.161 (0.403)	1.17	0.52-2.63
Sublingual vs. gum (0)		1.020 (0.383)	2.77	1.29-5.96	1.081 (0.494)	2.95	1.10-7.92
Lozenge vs. gum (1)		0.598 (0.240)	1.82	1.12-2.94	0.599 (0.379)	1.82	0.85-3.88
Spray vs. inhaler (0)		0.309 (0.350)	1.36	0.68-2.74	0.332 (0.453)	1.39	0.56-3.45
Sublingual vs. inhaler (0)		1.199 (0.437)	3.32	1.39-7.95	1.253 (0.546)	3.50	1.17-10.44
Lozenge vs. inhaler (0)		0.777 (0.319)	2.18	1.15-4.12	0.770 (0.487)	2.16	0.82-5.72

<b>Appendix 8d: Adverse events</b>							
<b>Comparison</b>	<b>P (%)</b>	<b>Classical (Fixed effects model)</b>			<b>Bayesian (Random effects model)</b>		
		<b>Log OR (SE)</b>	<b>OR</b>	<b>95% CI</b>	<b>Log OR (SE)</b>	<b>OR</b>	<b>95% CrI</b>
Sublingual vs. spray (0)		0.890 (0.408)	2.43	1.08-5.51	0.921 (0.532)	2.51	0.87-7.28
Lozenge vs. spray (0)		0.468 (0.278)	1.60	0.92-2.79	0.438 (0.465)	1.55	0.61-3.93
Lozenge vs. sublingual (0)		-0.422 (0.382)	0.66	0.31-1.41	-0.482 (0.546)	0.62	0.21-1.84
P(placebo is worst)	0.0						
P(patch is worst)	0.0						
P(bupropion is worst)	0.0						
P(varenicline is worst)	35.1						
P(gum is worst)	0.0						
P(inhaler is worst)	0.0						
P(spray is worst)	0.3						
P(sublingual is worst)	57.4						
P(lozenge is worst)	7.2						
Placebo rate (SE): 0.062 (0.008)							
<b>Upper abdominal pain</b>							
Patch vs. placebo (3)		-0.857 (0.484)	0.42	0.16-1.12	-0.484 (0.951)	0.62	0.09-4.13
Bupropion vs. placebo (1)		0.201 (0.500)	1.22	0.45-3.32	0.212 (1.497)	1.24	0.06-24.66
Varenicline vs. placebo (1)		0.185 (0.384)	1.20	0.56-2.60	0.527 (1.124)	1.69	0.18-16.05
Bupropion vs. patch (0)		1.058 (0.695)	2.88	0.72-11.57	0.696 (1.794)	2.01	0.06-72.52
Varenicline vs. patch (1)		1.042 (0.618)	2.84	0.82-9.75	1.012 (1.106)	2.75	0.30-25.12
Varenicline vs. bupropion (0)		-0.015 (0.630)	0.98	0.28-3.47	0.316 (1.892)	1.37	0.03-60.31
P(placebo is worst)	10.7						
P(patch is worst)	5.4						
P(bupropion is worst)	36.0						
P(varenicline is worst)	47.9						
Placebo rate (SE): 0.029 (0.025)							
<b>Gastrointestinal disturbance</b>							
Gum vs. placebo (5)		0.733 (0.083)	2.08	1.76-2.46	0.739 (0.209)	2.09	1.38-3.18
Varenicline vs. placebo (6)		0.744 (0.139)	2.11	1.60-2.78	0.770 (0.199)	2.16	1.45-3.22
Inhaler vs. placebo (2)		1.304 (0.252)	3.69	2.23-6.10	1.277 (0.360)	3.59	1.75-7.37

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Patch vs. placebo (2)		-0.154 (0.193)	0.86	0.58-1.26	-0.257 (0.352)	0.77	0.38-1.57
Sublingual vs. placebo (2)		0.754 (0.315)	2.12	1.13-3.99	0.773 (0.388)	2.17	1.00-4.71
Bupropion vs. placebo (4)		0.378 (0.198)	1.46	0.98-2.17	0.454 (0.272)	1.57	0.91-2.71
Lozenge vs. placebo (1)		0.584 (0.141)	1.79	1.35-2.38	0.717 (0.332)	2.05	1.06-3.98
Varenicline vs. gum (0)		0.011 (0.162)	1.01	0.73-1.40	0.031 (0.292)	1.03	0.58-1.85
Inhaler vs. gum (0)		0.571 (0.266)	1.77	1.04-3.01	0.539 (0.422)	1.71	0.74-3.98
Patch vs. gum (0)		-0.887 (0.210)	0.41	0.27-0.63	-0.996 (0.422)	0.37	0.16-0.86
Sublingual vs. gum (0)		0.020 (0.326)	1.02	0.53-1.96	0.035 (0.450)	1.04	0.42-2.55
Bupropion vs. gum (0)		-0.356 (0.214)	0.70	0.46-1.08	-0.285 (0.331)	0.75	0.39-1.46
Lozenge vs. gum (1)		-0.149 (0.164)	0.86	0.62-1.20	-0.021 (0.372)	0.98	0.47-2.06
Inhaler vs. varenicline (0)		0.560 (0.288)	1.75	0.98-3.11	0.508 (0.412)	1.66	0.73-3.79
Patch vs. varenicline (1)		-0.898 (0.238)	0.41	0.25-0.66	-1.026 (0.367)	0.36	0.17-0.75
Sublingual vs. varenicline (0)		0.009 (0.344)	1.01	0.51-2.01	0.004 (0.442)	1.00	0.41-2.43
Bupropion vs. varenicline (3)		-0.367 (0.241)	0.69	0.43-1.12	-0.316 (0.266)	0.73	0.43-1.24
Lozenge vs. varenicline (0)		-0.161 (0.198)	0.85	0.57-1.27	-0.052 (0.381)	0.95	0.44-2.03
Patch vs. inhaler (0)		-1.458 (0.318)	0.23	0.12-0.44	-1.534 (0.498)	0.22	0.08-0.58
Sublingual vs. inhaler (0)		-0.551 (0.404)	0.58	0.26-1.29	-0.504 (0.538)	0.60	0.21-1.77
Bupropion vs. inhaler (0)		-0.927 (0.320)	0.40	0.21-0.75	-0.824 (0.453)	0.44	0.18-1.09
Lozenge vs. inhaler (0)		-0.721 (0.289)	0.49	0.27-0.87	-0.560 (0.494)	0.57	0.21-1.53
Sublingual vs. patch (0)		0.907 (0.370)	2.48	1.18-5.19	1.030 (0.538)	2.80	0.96-8.22
Bupropion vs. patch (0)		0.531 (0.276)	1.70	0.98-2.96	0.710 (0.440)	2.03	0.84-4.90
Lozenge vs. patch (0)		0.737 (0.239)	2.09	1.30-3.37	0.974 (0.495)	2.65	0.98-7.13
Bupropion vs. sublingual (0)		-0.376 (0.372)	0.69	0.33-1.44	-0.320 (0.472)	0.73	0.28-1.87
Lozenge vs. sublingual (0)		-0.170 (0.345)	0.84	0.42-1.68	-0.056 (0.518)	0.95	0.34-2.67
Lozenge vs. bupropion (0)		0.206 (0.243)	1.23	0.76-2.00	0.264 (0.417)	1.30	0.57-3.00
P(placebo is worst)	0.0						
P(gum is worst)	3.5						
P(varenicline is worst)	3.5						
P(inhaler is worst)	71.7						

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(patch is worst)	0.0						
P(sublingual is worst)	13.9						
P(bupropion is worst)	0.5						
P(lozenge is worst)	6.9						
Placebo rate (SE): 0.067 (0.015)							
Constipation/diarrhea							
Bupropion vs. placebo (9)		1.001 (0.140)	2.72	2.05-3.60	1.069 (0.187)	2.91	2.00-4.23
Patch vs. placebo (4)		-0.232 (0.252)	0.79	0.48-1.31	-0.193 (0.334)	0.82	0.42-1.61
Varenicline vs. placebo (7)		0.848 (0.145)	2.34	1.75-3.12	0.896 (0.197)	2.45	1.65-3.63
Gum vs. placebo (1)		0.514 (1.132)	1.67	0.17-16.09	1.047 (1.423)	2.85	0.17-49.11
Lozenge vs. placebo (1)		0.408 (0.254)	1.50	0.91-2.50	0.403 (0.453)	1.50	0.60-3.70
Patch vs. bupropion (0)		-1.232 (0.289)	0.29	0.16-0.52	-1.262 (0.356)	0.28	0.14-0.58
Varenicline vs. bupropion (3)		-0.153 (0.202)	0.86	0.57-1.28	-0.173 (0.218)	0.84	0.54-1.30
Gum vs. bupropion (0)		-0.486 (1.140)	0.61	0.06-6.02	-0.022 (1.425)	0.98	0.06-16.90
Lozenge vs. bupropion (0)		-0.593 (0.290)	0.55	0.31-0.99	-0.666 (0.495)	0.51	0.19-1.38
Varenicline vs. patch (1)		1.080 (0.291)	2.94	1.65-5.27	1.089 (0.326)	2.97	1.55-5.70
Gum vs. patch (0)		0.746 (1.159)	2.11	0.21-21.43	1.240 (1.449)	3.46	0.19-62.66
Lozenge vs. patch (0)		0.640 (0.358)	1.90	0.93-3.88	0.596 (0.564)	1.82	0.59-5.61
Gum vs. varenicline (0)		-0.334 (1.141)	0.72	0.07-7.02	0.151 (1.433)	1.16	0.07-20.46
Lozenge vs. varenicline (0)		-0.440 (0.292)	0.64	0.36-1.15	-0.493 (0.493)	0.61	0.23-1.64
Lozenge vs. gum (0)		-0.107 (1.160)	0.90	0.09-9.14	-0.644 (1.484)	0.53	0.03-10.21
P(placebo is worst)	0.0						
P(bupropion is worst)	41.7						
P(patch is worst)	0.0						
P(varenicline is worst)	11.7						
P(gum is worst)	42.9						
P(lozenge is worst)	3.7						
Placebo rate (SE): 0.039 (0.010)							

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>Sleep disturbance</b>							
Patch vs. placebo (6)		0.915 (0.114)	2.50	1.99-3.14	0.607 (0.295)	1.83	1.02-3.31
Bupropion vs. placebo (7)		0.564 (0.110)	1.76	1.41-2.19	0.564 (0.277)	1.76	1.01-3.06
Varenicline vs. placebo (4)		0.654 (0.193)	1.92	1.31-2.83	0.779 (0.378)	2.18	1.02-4.64
Bupropion vs. patch (1)		-0.352 (0.158)	0.70	0.51-0.97	-0.043 (0.376)	0.96	0.45-2.03
Varenicline vs. patch (0)		-0.262 (0.224)	0.77	0.49-1.20	0.172 (0.474)	1.19	0.46-3.06
Varenicline vs. bupropion (2)		0.090 (0.222)	1.09	0.70-1.71	0.214 (0.412)	1.24	0.54-2.83
P(placebo is worst)	0.0						
P(patch is worst)	29.9						
P(bupropion is worst)	17.3						
P(varenicline is worst)	52.8						
Placebo rate (SE): 0.071 (0.018)							
<b>Insomnia</b>							
Bupropion vs. placebo (14)		0.883 (0.068)	2.42	2.11-2.77	0.911 (0.092)	2.49	2.07-2.99
Varenicline vs. placebo (8)		0.406 (0.084)	1.50	1.27-1.77	0.435 (0.115)	1.55	1.23-1.94
Patch vs. placebo (4)		0.218 (0.103)	1.24	1.01-1.53	0.229 (0.138)	1.26	0.95-1.66
Varenicline vs. bupropion (3)		-0.478 (0.108)	0.62	0.50-0.77	-0.476 (0.124)	0.62	0.49-0.80
Patch vs. bupropion (2)		-0.665 (0.123)	0.51	0.40-0.66	-0.682 (0.149)	0.51	0.38-0.68
Patch vs. varenicline (1)		-0.187 (0.132)	0.83	0.63-1.08	-0.206 (0.156)	0.81	0.60-1.11
P(placebo is worst)	0.0						
P(bupropion is worst)	100						
P(varenicline is worst)	0.0						
P(patch is worst)	0.0						
Placebo rate (SE): 0.113 (0.013)							
<b>Abnormal dreams</b>							
Patch vs. placebo (4)		0.693 (0.144)	2.00	1.50-2.67	1.088 (0.380)	2.97	1.39-6.35
Varenicline vs. placebo (6)		0.953 (0.131)	2.59	1.99-3.37	1.150 (0.307)	3.16	1.71-5.84
Bupropion vs. placebo (5)		0.160 (0.170)	1.17	0.84-1.65	0.373 (0.334)	1.45	0.74-2.83
Varenicline vs. patch (1)		0.260 (0.195)	1.30	0.88-1.92	0.062 (0.412)	1.06	0.47-2.43

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Bupropion vs. patch (1)		-0.532 (0.223)	0.59	0.38-0.92	-0.715 (0.425)	0.49	0.21-1.14
Bupropion vs. varenicline (3)		-0.793 (0.215)	0.45	0.29-0.70	-0.777 (0.349)	0.46	0.23-0.92
P(placebo is worst)	0.0						
P(patch is worst)	42.2						
P(varenicline is worst)	57.2						
P(bupropion is worst)	0.6						
Placebo rate (SE): 0.030 (0.011)							
Anxiety/irritability							
Bupropion vs. placebo (9)		0.079 (0.139)	1.08	0.82-1.43	0.127 (0.193)	1.14	0.77-1.67
Varenicline vs. placebo (5)		0.312 (0.158)	1.37	1.00-1.88	0.368 (0.232)	1.44	0.91-2.30
Patch vs. placebo (2)		-0.266 (0.237)	0.77	0.48-1.23	-0.261 (0.340)	0.77	0.39-1.52
Varenicline vs. bupropion (3)		0.233 (0.211)	1.26	0.83-1.92	0.241 (0.245)	1.27	0.78-2.08
Patch vs. bupropion (2)		-0.345 (0.275)	0.71	0.41-1.23	-0.387 (0.329)	0.68	0.35-1.31
Patch vs. varenicline (1)		-0.578 (0.285)	0.56	0.32-0.99	-0.628 (0.362)	0.53	0.26-1.10
P(placebo is worst)	2.3						
P(bupropion is worst)	13.3						
P(varenicline is worst)	81.6						
P(patch is worst)	2.8						
Placebo rate (SE): 0.042 (0.012)							
Asthenia/fatigue							
Bupropion vs. placebo (4)		-0.328 (0.238)	0.72	0.45-1.16	-0.319 (0.282)	0.73	0.41-1.28
Patch vs. placebo (2)		-0.737 (0.365)	0.48	0.23-0.99	-0.748 (0.434)	0.47	0.20-1.13
Varenicline vs. placebo (3)		0.191 (0.198)	1.21	0.81-1.80	0.200 (0.242)	1.22	0.75-1.98
Patch vs. bupropion (0)		-0.409 (0.435)	0.66	0.28-1.59	-0.429 (0.478)	0.65	0.25-1.69
Varenicline vs. bupropion (2)		0.520 (0.309)	1.68	0.91-3.12	0.519 (0.297)	1.68	0.93-3.04
Varenicline vs. patch (1)		0.928 (0.415)	2.53	1.10-5.81	0.948 (0.405)	2.58	1.15-5.80
P(placebo is worst)	16.8						
P(bupropion is worst)	2.1						
P(patch is worst)	0.9						

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(varenicline is worst)	80.2						
Placebo rate (SE): 0.051 (0.016)							
<b>Increased appetite</b>							
Varenicline vs. placebo (3)		0.509 (0.276)	1.66	0.96-2.89	0.519 (0.525)	1.68	0.59-4.80
Bupropion vs. placebo (1)		0.080 (0.441)	1.08	0.45-2.62	0.120 (0.821)	1.13	0.22-5.82
Patch vs. placebo (0)		0.754 (0.605)	2.12	0.63-7.13	0.850 (1.250)	2.34	0.19-28.52
Bupropion vs. varenicline (1)		-0.429 (0.520)	0.65	0.23-1.84	-0.399 (0.794)	0.67	0.14-3.28
Patch vs. varenicline (0)		0.244 (0.665)	1.28	0.34-4.83	0.331 (1.238)	1.39	0.12-16.55
Patch vs. bupropion (1)		0.674 (0.749)	1.96	0.44-8.77	0.730 (0.873)	2.08	0.36-11.89
P(placebo is worst)	4.5						
P(varenicline is worst)	33.1						
P(bupropion is worst)	3.5						
P(patch is worst)	58.9						
Placebo rate (SE): 0.053 (0.029)							
<b>Allergy</b>							
Bupropion vs. placebo (1)		0.902 (0.562)	2.46	0.80-7.59	0.934 (1.319)	2.54	0.18-35.6
Patch vs. placebo (1)		-0.054 (7.3e+4)	0.95	0.00-∞	-7.153 (67.35)	0.00	0.00-∞
Varenicline vs. placebo (1)		-0.543 (0.406)	0.58	0.26-1.31	-0.563 (1.209)	0.57	0.05-6.39
Patch vs. bupropion (0)		-0.956 (7.3e+4)	0.38	0.00-∞	-8.087 (67.39)	0.00	0.00-∞
Varenicline vs. bupropion (0)		-1.445 (0.693)	0.24	0.06-0.94	-1.497 (1.776)	0.22	0.01-7.81
Varenicline vs. patch (0)		-0.489 (7.3e+4)	0.61	0.00-∞	6.591 (67.38)	728	0.00-∞
P(placebo is worst)	7.6						
P(bupropion is worst)	38.4						
P(patch is worst)	47.7						
P(varenicline is worst)	6.3						
Placebo rate (SE): 0.036 (0.034)							
<b>Skin reactions</b>							
Patch vs. placebo (17)		1.157 (0.061)	3.18	2.81-3.60	1.136 (0.116)	3.11	2.47-3.93
Bupropion vs. placebo (2)		0.475 (0.211)	1.61	1.06-2.45	0.428 (0.349)	1.53	0.76-3.08

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Bupropion vs. patch (1)		-0.682 (0.219)	0.51	0.33-0.78	-0.708 (0.357)	0.49	0.24-1.01
P(placebo is worst)	0.0						
P(patch is worst)	97.5						
P(bupropion is worst)	2.5						
Placebo rate (SE): 0.090 (0.022)							
Sore/irritation throat							
Gum vs. placebo (5)		0.229 (0.166)	1.26	0.90-1.75	0.271 (0.332)	1.31	0.68-2.55
Inhaler vs. placebo (5)		1.228 (0.167)	3.42	2.44-4.77	1.240 (0.307)	3.45	1.87-6.39
Spray vs. placebo (3)		2.185 (0.212)	8.89	5.82-13.60	2.360 (0.419)	10.59	4.58-24.46
Bupropion vs. placebo (1)		-0.378 (0.296)	0.68	0.38-1.24	-0.384 (0.650)	0.68	0.19-2.50
Lozenge vs. placebo (1)		0.160 (0.253)	1.17	0.71-1.95	0.161 (0.624)	1.17	0.34-4.09
Patch vs. placebo (0)		-0.296 (0.273)	0.74	0.43-1.29	-0.128 (0.763)	0.88	0.19-4.05
Inhaler vs. gum(0)		0.999 (0.235)	2.71	1.70-4.35	0.969 (0.449)	2.63	1.07-6.47
Spray vs. gum (0)		1.956 (0.269)	7.07	4.13-12.12	2.089 (0.525)	8.07	2.83-23.07
Bupropion vs. gum (0)		-0.608 (0.340)	0.54	0.28-1.07	-0.655 (0.731)	0.52	0.12-2.24
Lozenge vs. gum (0)		-0.070 (0.303)	0.93	0.51-1.71	-0.110 (0.696)	0.90	0.22-3.60
Patch vs. gum (0)		-0.525 (0.320)	0.59	0.31-1.12	-0.399 (0.829)	0.67	0.13-3.52
Spray vs. inhaler (0)		0.957 (0.270)	2.60	1.52-4.47	1.120 (0.488)	3.07	1.15-8.14
Bupropion vs. inhaler (0)		-1.607 (0.340)	0.20	0.10-0.40	-1.624 (0.722)	0.20	0.05-0.84
Lozenge vs. inhaler (0)		-1.068 (0.304)	0.34	0.19-0.63	-1.079 (0.704)	0.34	0.08-1.39
Patch vs. inhaler (0)		-1.524 (0.320)	0.22	0.11-0.41	-1.367 (0.800)	0.25	0.05-1.26
Bupropion vs. spray (0)		-2.564 (0.365)	0.08	0.04-0.16	-2.744 (0.812)	0.06	0.01-0.33
Lozenge vs. spray (0)		-2.026 (0.331)	0.13	0.07-0.26	-2.200 (0.771)	0.11	0.02-0.52
Patch vs. spray (1)		-2.481 (0.346)	0.08	0.04-0.17	-2.487 (0.624)	0.08	0.02-0.29
Lozenge vs. bupropion (0)		0.538 (0.390)	1.71	0.79-3.74	0.545 (0.890)	1.72	0.29-10.22
Patch vs. bupropion (0)		0.083 (0.403)	1.09	0.49-2.43	0.257 (1.056)	1.29	0.16-10.68
Patch vs. lozenge (0)		-0.455 (0.373)	0.63	0.30-1.34	-0.288 (0.994)	0.75	0.10-5.47
P(placebo is worst)	0.0						
P(gum is worst)	0.0						

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(inhaler is worst)	1.0						
P(spray is worst)	98.1						
P(bupropion is worst)	0.1						
P(lozenge is worst)	0.5						
P(patch is worst)	0.3						
Placebo rate (SE): 0.152 (0.052)							
Dry mouth							
Bupropion vs. placebo (15)		0.638 (0.086)	1.89	1.59-2.25	0.691 (0.116)	2.00	1.58-2.52
Inhaler vs. placebo (1)		-0.173 (0.573)	0.84	0.27-2.65	-0.196 (0.654)	0.82	0.22-3.04
Patch vs. placebo (2)		-0.355 (0.234)	0.70	0.44-1.12	-0.360 (0.270)	0.70	0.41-1.20
Sublingual vs. placebo (1)		0.009 (0.467)	1.01	0.40-2.57	0.042 (0.529)	1.04	0.36-3.00
Varenicline vs. placebo (4)		0.200 (0.162)	1.22	0.88-1.69	0.238 (0.196)	1.27	0.86-1.88
Inhaler vs. bupropion (0)		-0.811 (0.580)	0.44	0.14-1.42	-0.887 (0.666)	0.41	0.11-1.56
Patch vs. bupropion (2)		-0.993 (0.249)	0.37	0.23-0.61	-1.051 (0.268)	0.35	0.20-0.60
Sublingual vs. bupropion (0)		-0.629 (0.475)	0.53	0.21-1.38	-0.649 (0.545)	0.52	0.18-1.56
Varenicline vs. bupropion (3)		-0.438 (0.183)	0.65	0.45-0.93	-0.453 (0.191)	0.64	0.43-0.93
Patch vs. inhaler (0)		-0.182 (0.619)	0.83	0.24-2.88	-0.164 (0.708)	0.85	0.21-3.50
Sublingual vs. inhaler (0)		0.182 (0.739)	1.20	0.27-5.26	0.238 (0.840)	1.27	0.24-6.81
Varenicline vs. inhaler (0)		0.373 (0.596)	1.45	0.44-4.78	0.434 (0.691)	1.54	0.39-6.15
Sublingual vs. patch (0)		0.364 (0.522)	1.44	0.51-4.09	0.402 (0.610)	1.49	0.44-5.06
Varenicline vs. patch (0)		0.555 (0.284)	1.74	0.99-3.07	0.598 (0.314)	1.82	0.97-3.41
Varenicline vs. sublingual(0)		0.191 (0.494)	1.21	0.45-3.25	0.196 (0.574)	1.22	0.39-3.83
P(placebo is worst)	0.0						
P(bupropion is worst)	80.1						
P(inhaler is worst)	8.5						
P(patch is worst)	0.0						
P(sublingual is worst)	10.8						
P(varenicline is worst)	0.6						
Placebo rate (SE): 0.066 (0.017)							

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>Mouth irritation (ulcer/canker sore)</b>							
Gum vs. placebo (6)		0.187 (0.195)	1.21	0.82-1.78	0.168 (0.372)	1.18	0.56-2.49
Bupropion vs. placebo (1)		0.599 (0.540)	1.82	0.62-5.36	0.622 (0.925)	1.86	0.29-11.84
Inhaler vs. placebo (1)		0.316 (0.288)	1.37	0.77-2.44	0.342 (0.728)	1.41	0.33-6.04
Lozenge vs. placebo (0)		0.185 (0.478)	1.20	0.46-3.13	0.199 (0.910)	1.22	0.20-7.52
Bupropion vs. gum (0)		0.412 (0.574)	1.51	0.48-4.76	0.454 (0.995)	1.57	0.22-11.51
Inhaler vs. gum (0)		0.129 (0.348)	1.14	0.57-2.28	0.174 (0.839)	1.19	0.22-6.36
Lozenge vs. gum (1)		-0.002 (0.516)	1.00	0.36-2.80	0.031 (0.794)	1.03	0.21-5.05
Inhaler vs. bupropion (0)		-0.283 (0.612)	0.75	0.22-2.56	-0.280 (1.225)	0.76	0.07-8.76
Lozenge vs. bupropion (0)		-0.414 (0.721)	0.66	0.16-2.80	-0.423 (1.283)	0.66	0.05-8.52
Lozenge vs. inhaler (0)		-0.131 (0.558)	0.88	0.29-2.68	-0.143 (1.168)	0.87	0.08-8.96
P(placebo is worst)	1.2						
P(gum is worst)	6.2						
P(bupropion is worst)	47.4						
P(inhaler is worst)	23.8						
P(lozenge is worst)	21.4						
Placebo rate (SE): 0.074 (0.040)							
<b>Oral discomfort/jaw soreness</b>							
Gum vs. placebo (4)		-0.330 (0.207)	0.72	0.48-1.09	0.281 (0.730)	1.32	0.31-5.70
Inhaler vs. placebo (1)		0.446 (0.432)	1.56	0.66-3.71	0.404 (1.231)	1.50	0.13-17.56
Sublingual vs. placebo (1)		0.063 (0.325)	1.07	0.56-2.04	0.011 (1.289)	1.01	0.08-13.31
Inhaler vs. gum (0)		0.776 (0.479)	2.17	0.83-5.67	0.123 (1.443)	1.13	0.06-20.27
Sublingual vs. gum (0)		0.394 (0.385)	1.48	0.69-3.20	-0.270 (1.491)	0.76	0.04-15.05
Sublingual vs. inhaler (0)		-0.383 (0.541)	0.68	0.23-2.01	-0.393 (1.740)	0.68	0.02-21.93
P(placebo is worst)	6.1						
P(gum is worst)	26.2						
P(inhaler is worst)	43.1						
P(sublingual is worst)	24.6						
Placebo rate (SE): 0.104 (0.068)							

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>Hiccups</b>							
Gum vs. placebo (5)		1.782 (0.306)	5.94	3.22-10.97	3.027 (0.955)	20.65	3.1-1.4e+2
Sublingual vs. placebo (2)		3.616 (1.020)	37.2	4.83-285.9	4.584 (1.793)	97.86	2.71-4e+3
Inhaler vs. placebo (1)		18.82 (4.2e+3)	1.5e+8	0-∞	45.46 (35.86)	5.5e+19	0-∞
Lozenge vs. placebo (1)		4.664 (1.026)	1.0e+2	13.6-825.5	6.310 (1.869)	5.5e+2	13.1-2e+4
Sublingual vs. gum (0)		1.833 (1.065)	6.25	0.74-52.6	1.556 (1.952)	4.74	0.1-2.4e+2
Inhaler vs. gum (0)		17.04 (4.2e+3)	2.5e+7	0-∞	42.43-35.89	2.7e+18	0-∞
Lozenge vs. gum (1)		2.881 (1.071)	17.8	2.09-151.9	3.283 (1.765)	26.65	0.8-9.1e+2
Inhaler vs. sublingual (0)		15.21 (4.2e+3)	4.0e+6	2.09-151.9	40.88 (35.94)	5.7e+17	0-∞
Lozenge vs. sublingual (0)		1.048 (1.447)	2.85	0.16-51.51	1.727 (2.552)	5.62	0.0-9.3e+2
Lozenge vs. inhaler (0)		-14.16 (4.2e+3)	0.0	0-∞	-39.15 (35.95)	0.0	0-∞
P(placebo is worst)	0.0						
P(gum is worst)	0.1						
P(sublingual is worst)	2.1						
P(inhaler is worst)	92.1						
P(lozenge is worst)	5.7						
Placebo rate (SE): 0.004 (0.003)							
<b>Excessive salivation</b>							
Gum vs. placebo (1)		0.357 (0.281)	1.43	0.81-2.51	0.348 (0.280)	1.42	0.81-2.48
P(placebo is worst)	11.7						
P(gum is worst)	88.3						
Placebo rate (SE): none							
<b>Coughing</b>							
Inhaler vs. placebo (5)		1.351 (0.179)	3.86	2.70-5.53	1.380 (0.311)	3.98	2.14-7.40
Spray vs. placebo (3)		1.557 (0.173)	4.75	3.35-6.71	1.547 (0.323)	4.70	2.46-8.96
Bupropion vs. placebo (1)		-0.595 (0.305)	0.55	0.30-1.02	-0.594 (0.591)	0.55	0.17-1.80
Lozenge vs. placebo (1)		0.587 (0.255)	1.80	1.08-3.00	0.604 (0.562)	1.83	0.59-5.63
Patch vs. placebo (1)		19.36 (7.0e+3)	2.6e+8	0.00-∞	82.51 (50.76)	6.8e+35	0.00-∞
Sublingual vs. placebo (1)		-19.41 (7.0e+3)	0.0	0.00-∞	-87.09 (68.26)	0.0	0.00-∞

Appendix 8d: Adverse events							
Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Spray vs. inhaler (0)		0.206 (0.249)	1.23	0.75-2.02	0.167 (0.426)	1.18	0.50-2.77
Bupropion vs. inhaler (0)		-1.946 (0.354)	0.14	0.07-0.29	-1.974 (0.678)	0.14	0.04-0.54
Lozenge vs. inhaler (0)		-0.764 (0.312)	0.47	0.25-0.87	-0.776 (0.637)	0.46	0.13-1.65
Patch vs. inhaler (0)		18.01 (7.0e+3)	6.6e+7	0.00-∞	81.13 (50.74)	1.7e+35	0.00-∞
Sublingual vs. inhaler (0)		-20.76 (7.0e+3)	0.0	0.00-∞	-88.47 (68.25)	0.0	0.00-∞
Bupropion vs. spray (0)		-2.152 (0.351)	0.12	0.06-0.23	-2.141 (0.700)	0.12	0.03-0.48
Lozenge vs. spray (0)		-0.970 (0.308)	0.38	0.20-0.70	-0.943 (0.655)	0.39	0.10-1.44
Patch vs. spray (0)		17.80 (7.0e+3)	5.4e+7	0.00-∞	80.96 (50.75)	1.5e+35	0.00-∞
Sublingual vs. spray (0)		-20.96 (7.0e+3)	0.0	0.00-∞	-88.64 (68.25)	0.0	0.00-∞
Lozenge vs. bupropion (0)		1.182 (0.398)	3.26	1.47-7.22	1.198 (0.846)	3.31	0.61-17.98
Patch vs. bupropion (0)		19.96 (7.0e+3)	4.6e+8	0.00-∞	83.11 (50.77)	1.2e+36	0.00-∞
Sublingual vs. bupropion (0)		-18.81 (7.0e+3)	0.0	0.00-∞	-86.50 (68.25)	0.0	0.00-∞
Patch vs. lozenge (0)		18.77 (7.0e+3)	1.4e+8	0.00-∞	81.91 (50.76)	3.7e+35	0.00-∞
Sublingual vs. lozenge (0)		-19.99 (7.0e+3)	0.0	0.00-∞	-87.70 (68.25)	0.0	0.00-∞
Sublingual vs. patch (0)		-38.77 (9.9e+3)	0.0	0.00-∞	-169.6 (74.37)	0.0	0.00-∞
P(placebo is worst)	0.0						
P(inhaler is worst)	0.3						
P(spray is worst)	0.4						
P(bupropion is worst)	0.0						
P(lozenge is worst)	0.0						
P(patch is worst)	99.3						
P(sublingual is worst)	0.0						
Placebo rate (SE): 0.075 (0.035)							
Nasal irritation							
Spray vs. placebo (3)		0.601 (0.344)	1.82	0.92-3.63	0.308 (0.854)	1.36	0.25-7.50
Patch vs. placebo (0)		-1.069 (0.377)	0.34	0.16-0.73	-1.329 (1.379)	0.26	0.02-4.18
Patch vs. spray (1)		-1.670 (0.510)	0.19	0.07-0.52	-1.637 (1.140)	0.19	0.02-1.90
P(placebo is worst)	28.7						

<b>Appendix 8d: Adverse events</b>							
<b>Comparison</b>	<b>P (%)</b>	<b>Classical (Fixed effects model)</b>			<b>Bayesian (Random effects model)</b>		
		<b>Log OR (SE)</b>	<b>OR</b>	<b>95% CI</b>	<b>Log OR (SE)</b>	<b>OR</b>	<b>95% CrI</b>
P(spray is worst)	65.3						
P(patch is worst)	6.0						
Placebo rate (SE): 0.956 (0.051)							
<b>Runny nose</b>							
Spray vs. placebo (3)		1.374 (0.305)	3.95	2.15-7.27	2.086 (0.998)	8.05	1.09-59.28
P(placebo is worst)	1.2						
P(spray is worst)	98.8						
Placebo rate (SE): 0.866 (0.095)							
<b>Sneezing</b>							
Spray vs. placebo (3)		1.706 (0.187)	5.51	3.79-8.01	1.752 (0.508)	5.77	2.09-15.94
Patch vs. placebo (0)		0.445 (0.238)	1.56	0.97-2.51	0.470 (1.092)	1.60	0.18-14.22
Patch vs. spray (1)		-1.261 (0.303)	0.28	0.15-0.52	-1.282 (0.904)	0.28	0.05-1.69
P(placebo is worst)	0.5						
P(spray is worst)	93.6						
P(patch is worst)	5.9						
Placebo rate (SE): 0.525 (0.087)							
<b>Eye watering</b>							
Spray vs. placebo (3)		1.911-0.222	6.76	4.33-10.54	2.056 (0.671)	7.82	2.04-29.92
Patch vs. placebo (0)		0.208-0.276	1.23	0.71-2.14	0.411 (1.215)	1.51	0.13-17.12
Patch vs. spray (1)		-1.703-0.354	0.18	0.09-0.37	-1.645 (1.045)	0.19	0.02-1.56
P(placebo is worst)	0.1						
P(spray is worst)	94.9						
P(patch is worst)	5.0						
Placebo rate (SE): 0.618 (0.129)							
<b>Blurred vision</b>							
Bupropion vs. placebo (2)		1.137 (0.561)	3.12	1.02-9.57	1.236 (0.916)	3.44	0.55-21.49
P(placebo is worst)	7.3						
P(bupropion is worst)	92.7						
Placebo rate (SE): 0.100 (0.101)							

<b>Appendix 8d: Adverse events</b>							
<b>Comparison</b>	<b>P (%)</b>	<b>Classical (Fixed effects model)</b>			<b>Bayesian (Random effects model)</b>		
		<b>Log OR (SE)</b>	<b>OR</b>	<b>95% CI</b>	<b>Log OR (SE)</b>	<b>OR</b>	<b>95% CrI</b>
<b>Irregular heart beat</b>							
Bupropion vs. placebo (1)		1.435 (0.915)	4.20	0.67-26.21	1.353 (0.910)	3.87	0.63-23.86
P(placebo is worst)	5.2						
P(bupropion is worst)	94.8						
Placebo rate (SE): none							

CI: confidence interval; CrI: credible interval; OR: odds ratio; P: probability; SE: standard error

**Appendix 8e: Adding behavioural support to pharmacotherapy for smoking cessation in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>Nicotine patch ± behaviour</b>							
<i><b>CAR at 6 m</b></i>							
Patch + behaviour vs. patch (1)		0.170 (0.257)	1.19	0.71-1.98	0.150 (0.261)	1.16	0.69-1.96
P(patch is best)	27.5						
P(patch + behaviour is best)	72.5						
<i><b>CAR at 1 y</b></i>							
Patch + behaviour vs. patch (1)		-0.026 (0.282)	0.97	0.55-1.71	-0.039 (0.287)	0.96	0.54-1.70
P(patch is best)	53.9						
P(patch + behaviour is best)	46.1						
<i><b>PPA at 6 m</b></i>							
Patch + behaviour vs. patch (3)		0.423 (0.172)	1.53	1.08-2.15	0.473 (0.480)	1.61	0.61-4.20
P(patch is best)	9.7						
P(patch + behaviour is best)	90.3						
<i><b>PPA at 1 y</b></i>							
Patch + behaviour vs. patch (3)		0.280 (0.175)	1.32	0.93-1.87	0.367 (0.533)	1.44	0.50-4.19
P(patch is best)	17.6						
P(patch + behaviour is best)	82.4						
<b>Nicotine gum ± behaviour</b>							
<i><b>PPA at 6 m</b></i>							
Gum + behaviour vs. gum (4)		0.123 (0.160)	1.13	0.82-1.56	0.124 (0.383)	1.13	0.53-2.43
P(gum is best)	33.6						
P(gum + behaviour is best)	66.4						
<i><b>PPA at 1 y</b></i>							
Gum + behaviour vs. gum (5)		0.005 (0.164)	1.01	0.72-1.40	0.020 (0.380)	1.02	0.48-2.18
P(gum is best)	45.7						
P(gum + behaviour is best)	54.3						

**Appendix 8e: Adding behavioural support to pharmacotherapy for smoking cessation in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>Behaviour ± NRT</b>							
<b><i>CAR at 6 m</i></b>							
Behaviour + gum vs. behaviour (3)		0.228 (0.173)	1.26	0.89-1.78	0.135 (0.440)	1.14	0.48-2.76
P(behaviour is best)	32.0						
P(behaviour + gum is best)	68.0						
<b><i>CAR at 1 y</i></b>							
Behaviour + gum vs. behaviour (3)		0.120 (0.190)	1.13	0.77-1.65	0.071 (0.485)	1.07	0.41-2.83
P(behaviour is best)	37.6						
P(behaviour + gum is best)	62.4						
<b><i>PAR at 1 y</i></b>							
Behaviour + gum vs. behaviour (1)		0.211 (0.471)	1.23	0.48-3.17	0.185 (0.478)	1.20	0.46-3.13
P(behaviour is best)	34.2						
P(behaviour + gum is best)	65.8						
<b><i>PPA at 6 m</i></b>							
Behaviour + gum vs. behaviour (6)		0.330 (0.135)	1.39	1.06-1.82	0.212 (0.353)	1.24	0.61-2.50
Behaviour + patch vs. behaviour (1)		0.762 (0.562)	2.14	0.70-6.60	0.838 (0.910)	2.31	0.38-14.26
Behaviour + patch vs. behaviour + gum (0)		0.432 (0.578)	1.54	0.48-4.90	0.626 (1.000)	1.87	0.25-13.80
P(behaviour is best)	3.1						
P(behaviour + gum is best)	21.3						
P(behaviour + patch is best)	75.6						
<b><i>PPA at 1 y</i></b>							
Behaviour + gum vs. behaviour (7)		0.328 (0.134)	1.39	1.06-1.81	0.291 (0.197)	1.34	0.90-1.98
Behaviour + patch vs. behaviour (1)		0.762 (0.562)	2.14	0.70-6.60	0.803 (0.674)	2.23	0.58-8.59
Behaviour + patch vs. behaviour + gum (0)		0.434 (0.578)	1.54	0.49-4.91	0.512 (0.706)	1.67	0.41-6.85
P(behaviour is best)	1.1						
P(behaviour + gum is best)	22.4						

**Appendix 8e: Adding behavioural support to pharmacotherapy for smoking cessation in relatively healthy and motivated-to-quit populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(behaviour + patch is best)	76.5						
<b><i>Relapse at 1 y</i></b> <sup>§</sup>							
Behaviour + gum vs. behaviour (3)		0.724 (0.191)	2.06	1.41-3.03	0.633 (0.545)	1.88	0.63-5.61
P(behaviour is worst)	9.4						
P(behaviour + gum is worst)	90.6						

§ relapse = proportion of quitters at 3 months was detected as smokers at 1 year;

CAR: continuous abstinence rate; CI: confidence interval; CrI: credible interval; m: month; OR: odds ratio; P: probability; PAR: prolonged abstinence rate; PPA: point prevalence abstinence; SE: standard error; y: year

**Appendix 8f: Pharmacotherapy for smoking cessation in specific populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>Adolescent</b>							
<b><i>PPA at 6 m</i></b>							
Bupropion vs. placebo (1)		-0.107 (0.522)	0.90	0.32-2.55	-0.080 (1.250)	0.92	0.08-11.24
NRT vs. placebo (1)		1.108 (0.795)	3.03	0.62-14.85	1.292 (1.403)	3.64	0.22-60.19
NRT vs. bupropion (0)		1.216 (0.951)	3.37	0.50-22.60	1.372 (1.867)	3.94	0.09-165.00
P(placebo is best)	8.4						
P(bupropion is best)	17.5						
P(NRT is best)	74.1						
Placebo rate (SE): 0.062 (0.051)							
<b>Cardiovascular or smoking-related disease</b>							
<b><i>CAR at 6 m</i></b>							
NRT vs. placebo (2)		0.696 (0.263)	2.01	1.19-3.39	0.680 (0.691)	1.97	0.50-7.86
Bupropion vs. placebo (1)		1.118 (0.222)	3.06	1.96-4.77	1.128 (0.957)	3.09	0.46-20.96
Bupropion vs. NRT (0)		0.422 (0.344)	1.53	0.77-3.04	0.449 (1.132)	1.57	0.16-15.08
P(placebo is best)	2.8						
P(NRT is best)	26.2						
P(bupropion is best)	71.0						
Placebo rate (SE): 0.127 (0.074)							
<b><i>CAR at 1 y</i></b>							
NRT vs. placebo (2)		0.841 (0.310)	2.32	1.25-4.31	0.977 (0.734)	2.66	0.61-11.52
Bupropion vs. placebo (1)		1.057 (0.240)	2.88	1.78-4.66	1.035 (0.980)	2.82	0.40-20.00
Bupropion vs. NRT (0)		0.217 (0.392)	1.24	0.57-2.72	0.058 (1.200)	1.06	0.10-11.67
P(placebo is best)	1.3						
P(NRT is best)	43.0						
P(bupropion is best)	55.7						
Placebo rate (SE): 0.088 (0.069)							
<b><i>PAR at 6 m</i></b>							
NRT vs. placebo (1)		0.729 (0.379)	2.07	0.97-4.42	0.727 (0.360)	2.07	1.01-4.25
P(placebo is best)	1.0						
P(NRT is best)	99.0						

**Appendix 8f: Pharmacotherapy for smoking cessation in specific populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
Placebo rate (SE): none							
<b>PAR at 1 y</b>							
NRT vs. placebo (1)		1.124 (0.619)	3.08	0.89-10.61	1.078 (0.592)	2.94	0.90-9.60
P(placebo is best)	2.0						
P(NRT is best)	98.0						
Placebo rate (SE): none							
<b>PPA at 6 m</b>							
Bupropion vs. placebo (1)		1.310 (0.210)	3.71	2.43-5.64	1.296 (0.210)	3.66	2.40-5.57
P(placebo is best)	0.0						
P(bupropion is best)	100.0						
Placebo rate (SE): none							
<b>PPA at 1 y</b>							
Bupropion vs. placebo (1)		0.992 (0.215)	2.70	1.76-4.15	1.020 (1.153)	2.77	0.28-27.83
NRT vs. placebo (1)		0.702 (0.425)	2.02	0.86-4.72	0.752 (1.224)	2.12	0.18-24.56
NRT vs. bupropion (0)		-0.290 (0.476)	0.75	0.29-1.94	-0.267 (1.611)	0.77	0.03-19.19
P(placebo is best)	5.3						
P(bupropion is best)	57.3						
P(NRT is best)	37.4						
Placebo rate (SE): 0.107 (0.080)							
<b>Relapse at 1 y<sup>s</sup></b>							
NRT vs. placebo (2)		0.507 (0.277)	1.66	0.95-2.89	0.531 (0.694)	1.70	0.42-6.81
Bupropion vs. placebo (1)		0.730 (0.294)	2.07	1.15-3.74	0.725(0.941)	2.06	0.31-13.57
Bupropion vs. NRT (0)		0.223 (0.404)	1.25	0.56-2.81	0.194 (1.175)	1.21	0.12-12.73
P(placebo is worst)	3.7						
P(NRT is worst)	37.4						
P(bupropion is worst)	58.9						
Placebo rate (SE): 0.094 (0.052)							
<b>Depression</b>							
<b>CAR at 1 y</b>							
NRT vs. placebo (1)		1.075 (0.572)	2.93	0.93-9.20	1.080 (0.556)	2.94	0.97-8.94

**Appendix 8f: Pharmacotherapy for smoking cessation in specific populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
P(placebo is best)	2.2						
P(NRT is best)	97.8						
Placebo rate (SE): none							
<b>PPA at 6 m</b>							
NRT vs. placebo (1)		-0.588 (0.685)	0.56	0.14-2.19	-0.638 (0.699)	0.53	0.13-2.14
P(placebo is best)	82.8						
P(NRT is best)	17.2						
Placebo rate (SE): none							
<b>PPA at 1 y</b>							
NRT vs. placebo (2)		-0.444 (0.551)	0.64	0.21-1.93	-0.413 (0.925)	0.66	0.10-4.21
Bupropion vs. placebo (1)		1.411 (0.634)	4.10	1.15-14.55	1.516 (1.172)	4.55	0.44-47.51
Bupropion vs. NRT (1)		1.855 (0.839)	6.39	1.19-34.25	1.929 (1.096)	6.89	0.77-61.68
P(placebo is best)	6.8						
P(NRT is best)	2.5						
P(bupropion is best)	90.7						
Placebo rate (SE): 0.197 (0.138)							
<b>Hospitalized</b>							
<b>CAR at 6 m</b>							
Bupropion vs. placebo (1)		-0.600 (0.571)	0.55	0.17-1.72	-0.622 (0.564)	0.54	0.17-1.66
P(placebo is best)	87.3						
P(bupropion is best)	12.7						
Placebo rate (SE): none							
<b>CAR at 1 y</b>							
Bupropion vs. placebo (1)		0.463 (0.344)	1.59	0.80-3.16	0.445 (1.217)	1.56	0.14-17.77
NRT vs. placebo (1)		0.459 (0.348)	1.58	0.79-3.18	0.471 (1.160)	1.60	0.16-16.29
NRT vs. bupropion (0)		-0.004 (0.489)	1.00	0.37-2.65	0.026 (1.682)	1.03	0.04-29.69
P(placebo is best)	10.6						
P(bupropion is best)	45.4						
P(NRT is best)	44.0						
Placebo rate (SE): 0.149 (0.078)							

**Appendix 8f: Pharmacotherapy for smoking cessation in specific populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>PPA at 6 m</b>							
NRT vs. placebo (1)		0.441 (0.672)	1.55	0.41-5.96	0.388 (0.663)	1.47	0.39-5.55
P(placebo is best)	27.4						
P(NRT is best)	72.6						
Placebo rate (SE): none							
<b>PPA at 1 y</b>							
Bupropion vs. placebo (1)		0.228 (0.303)	1.26	0.69-2.30	0.223 (0.305)	1.25	0.68-2.30
P(placebo is best)	23.8						
P(bupropion is best)	76.2						
Placebo rate (SE): none							
<b>Relapse at 1 y<sup>§</sup></b>							
Bupropion vs. placebo (1)		0.218 (0.469)	1.24	0.49-3.18	0.244 (1.282)	1.28	0.10-16.58
NRT vs. placebo (1)		0.038 (0.416)	1.04	0.45-2.39	0.059 (1.213)	1.06	0.09-12.01
NRT vs. bupropion (0)		-0.180 (0.627)	0.84	0.24-2.93	-0.184 (1.711)	0.83	0.03-25.47
P(placebo is worst)	20.6						
P(bupropion is worst)	45.0						
P(NRT is worst)	34.4						
Placebo rate (SE): 0.102 (0.069)							
<b>Mental disorders</b>							
<b>PPA at 6 m</b>							
Bupropion vs. placebo (3)		1.037 (0.870)	2.82	0.50-16.08	1.374 (1.210)	3.95	0.35-44.48
P(placebo is best)	11.6						
P(bupropion is best)	88.4						
Placebo rate (SE): 0.038 (0.038)							
<b>PPA at 2 y</b>							
Bupropion vs. placebo (1)		0.000 (1.134)	1.00	0.10-9.66	-0.095 (1.091)	0.91	0.10-8.06
P(placebo is best)	52.5						
P(bupropion is best)	47.5						
Placebo rate (SE): none							

**Appendix 8f: Pharmacotherapy for smoking cessation in specific populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>COPD</b>							
<b><i>CAR at 6 m</i></b>							
Bupropion vs. placebo (2)		0.706 (0.243)	2.03	1.25-3.30	0.728 (0.700)	2.07	0.51-8.40
P(placebo is best)	8.9						
P(bupropion is best)	91.1						
Placebo rate (SE): 0.132 (0.088)							
<b><i>CAR at 1 y</i></b>							
NRT vs. placebo (1)		1.051 (0.388)	2.86	1.32-6.22	1.018 (0.392)	2.77	1.26-6.06
P(placebo is best)	0.4						
P(NRT is best)	99.6						
Placebo rate (SE): none							
<b><i>PPA at 6 m</i></b>							
Bupropion vs. placebo (2)		0.505 (0.207)	1.66	1.09-2.51	0.534 (0.664)	1.71	0.45-6.44
NRT vs. placebo (1)		1.033 (0.303)	2.81	1.53-5.15	1.090 (0.888)	2.97	0.50-17.55
NRT vs. bupropion (0)		0.528 (0.367)	1.70	0.81-3.54	0.556 (1.113)	1.74	0.19-16.14
P(placebo is best)	1.6						
P(bupropion is best)	21.5						
P(NRT is best)	76.9						
Placebo rate (SE): 0.153 (0.067)							
<b><i>PPA at 1 y</i></b>							
NRT vs. placebo (1)		0.663 (0.315)	1.94	1.03-3.64	0.670 (0.312)	1.95	1.05-3.65
P(placebo is best)	1.6						
P(NRT is best)	98.4						
Placebo rate (SE): none							
<b>Pregnant</b>							
<b><i>CAR at 1 y</i></b>							
NRT vs. placebo (1)		0.082 (0.356)	1.09	0.53-2.21	0.068 (0.349)	1.07	0.53-2.15
P(placebo is best)	44.3						
P(NRT is best)	55.7						
Placebo rate (SE): none							

**Appendix 8f: Pharmacotherapy for smoking cessation in specific populations**

Comparison	P (%)	Classical (Fixed effects model)			Bayesian (Random effects model)		
		Log OR (SE)	OR	95% CI	Log OR (SE)	OR	95% CrI
<b>PPA at 6 m</b>							
NRT vs. placebo (1)		0.155 (0.474)	1.17	0.45-3.01	0.137 (0.487)	1.15	0.43-3.04
P(placebo is best)	39.9						
P(NRT is best)	60.1						
Placebo rate (SE): none							
<b>Relapse at 1 y<sup>§</sup></b>							
NRT vs. placebo (1)		0.370 (0.600)	1.45	0.44-4.80	0.301 (0.589)	1.35	0.42-4.39
P(placebo is worst)	31.3						
P(NRT is worst)	68.7						
Placebo rate (SE): none							
<b>Substance abuse</b>							
<b>CAR at 6 m</b>							
NRT vs. placebo (1)		1.713 (0.664)	5.54	1.47-20.93	1.694 (0.662)	5.44	1.45-20.47
P(placebo is best)	0.1						
P(NRT is best)	99.9						
Placebo rate (SE): none							
<b>Stress</b>							
<b>PPA at 6 m</b>							
Bupropion vs. placebo (1)		0.981 (1.291)	2.67	0.20-35.26	0.819 (1.227)	2.27	0.20-26.35
P(placebo is best)	25.1						
P(bupropion is best)	74.9						
Placebo rate (SE): none							

§ relapse = proportion of quitters at 3 months was detected as smokers at 1 year

CAR: continuous abstinence rate; CI: confidence interval; CrI: credible interval; m: month; OR: odds ratio; P: probability; PAR: prolonged abstinence rate; PPA: point prevalence abstinence; SE: standard error; y: year

## APPENDIX 9: DATA EXTRACTION FORM FOR ECONOMIC STUDIES

Data extraction form for economic studies <sup>212</sup>	
Author, year of publication	
Country	
Population	
Intervention(s)	
Comparator(s)	
Outcome measured	
Study design	
Time horizon	
Study perspective	
Currency year	
Health states considered	
Major assumptions	
Healthcare resources considered and source	
Other resources considered and source	
Quit rate and source	
Relapse rate and source	
Price elasticity of demand* for smoking cessation interventions	
Other parameters	
Any Canadian data source [specify]	
Discounting	
Assessment of uncertainty	
Major sensitive parameters	
Study results	
Conclusions	
Key study considerations stated	
Sponsorship	
Comment	

\* Defined as the ratio of the percentage change in quantity demanded over the percentage change in price<sup>214</sup>

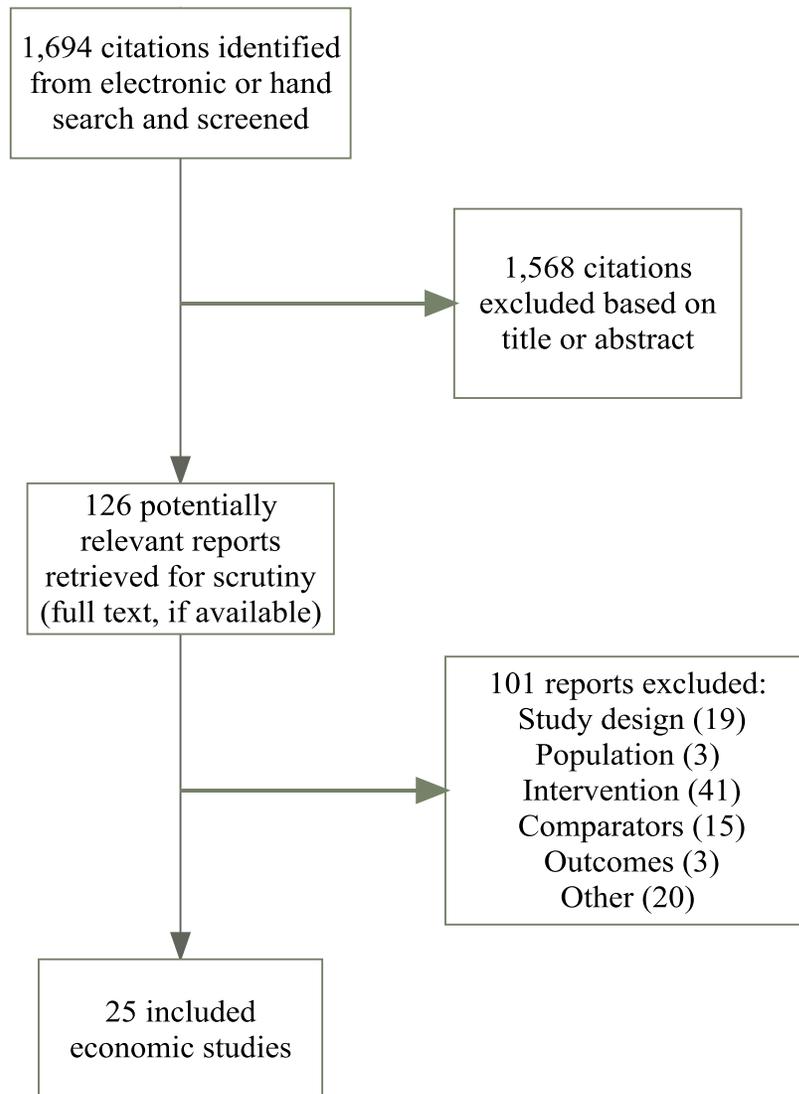
## APPENDIX 10: EXCLUDED ECONOMIC STUDIES

List of excluded economic studies		
Authors	Year	Reason for exclusion
AHCRP <sup>386</sup>	1998	Other
AKEHURST et al <sup>387</sup>	1994	Comparators
ALTERMAN et al <sup>123</sup>	2001	Outcomes
AN et al <sup>280</sup>	2006	Comparators
ANTONANZAS et al <sup>388</sup>	2003	Other
AVEYARD et al <sup>389</sup>	2008	Study Design
BALA <sup>390</sup>	2004	Study Design
BARENDREGT et al <sup>391</sup>	1998	Other
BASKA et al <sup>392</sup>	2004	Study Design
BEMELMANS et al <sup>393</sup>	2006	Study Design
BUCK et al <sup>394</sup>	2000	Intervention
CHEUNG et al <sup>395</sup>	1997	Study Design
CORNUZ et al <sup>396</sup>	2003	Other
COVINGTON et al <sup>397</sup>	2005	Study Design
CREALEY et al <sup>398</sup>	1998	Intervention
CROGHAN et al <sup>399</sup>	1997	Intervention
CROMWELL et al <sup>400</sup>	1997	Comparators
CUMMINGS et al <sup>401</sup>	2006	Intervention
CURRY et al <sup>288</sup>	1998	Study Design
DEY et al <sup>402</sup>	1999	Study Design
EMMONS et al <sup>198</sup>	2005	Population
ETTER <sup>403</sup>	2002	Study Design
FELLOWS et al <sup>404</sup>	2007	Comparators
FERNANDEZ DE BOBADILLIA et al <sup>405</sup>	2008	Other
FERRANTE et al <sup>406</sup>	2007	Intervention
FISCELLA et al <sup>407</sup>	1996	Intervention
GILBERT et al <sup>208</sup>	2004	Other
GODFREY et al <sup>408</sup>	2005	Intervention
GONZALEZ-ENRIQUEZ et al <sup>409</sup>	2002	Other
GORECKA <sup>410</sup>	2004	Other
GOSNEY <sup>411</sup>	2001	Study Design
HALPERN et al <sup>412</sup>	2007	Study Design
HALPIN et al <sup>413</sup>	2006	Intervention
HOLLIS et al <sup>414</sup>	2007	Comparators
HUESTON et al <sup>415</sup>	1994	Intervention
HURLEY <sup>416</sup>	2005	Intervention
HURLEY et al <sup>417</sup>	2007	Intervention
JAVITZ et al <sup>418</sup>	2004	Comparators
JAVITZ et al <sup>419</sup>	2004	Other
JAVITZ et al <sup>418</sup>	2004	Other (duplicate)
JOHANSSON et al <sup>420</sup>	2005	Intervention
JOHNSON et al <sup>421</sup>	2004	Study Design
KAPER <sup>422</sup>	2007	Other

<b>List of excluded economic studies</b>		
<b>Authors</b>	<b>Year</b>	<b>Reason for exclusion</b>
KAPER et al <sup>195</sup>	2005	Study Design
KRUMHOLZ et al <sup>423</sup>	1993	Intervention
LAGRUE et al <sup>424</sup>	1991	Other
LAW et al <sup>425</sup>	1995	Study Design
LAWRENCE et al <sup>426</sup>	1998	Outcomes
LENNOX et al <sup>427</sup>	2001	Intervention
LEVITON <sup>428</sup>	1989	Intervention
LEVY <sup>429</sup>	2006	Intervention
LEVY et al <sup>430</sup>	2002	Intervention
LIGHTWOOD et al <sup>431</sup>	1997	Intervention
LIGHTWOOD et al <sup>431</sup>	1997	Other (duplicate)
LOWIN <sup>432</sup>	1996	Comparators
MCALISTER et al <sup>433</sup>	2004	Intervention
MILLER et al <sup>199</sup>	1996	Population
NIELSEN et al <sup>221</sup>	2000	Other (duplicate)
OLSEN et al <sup>434</sup>	2006	Comparators
ONG et al <sup>435</sup>	2005	Comparators
ORME et al <sup>238</sup>	2001	Intervention
OSTER et al <sup>436</sup>	1986	Comparators
OSTER et al <sup>437</sup>	1984	Intervention
OSTER et al <sup>438</sup>	1996	Study Design
PARROTT <sup>439</sup>	2007	Study Design
PHILLIPS et al <sup>440</sup>	1993	Intervention
PLANS et al <sup>441</sup>	1995	Other
PLANSRUBIO <sup>442</sup>	1998	Other
PLANS-RUBIO <sup>443</sup>	1998	Other
POLLACK <sup>444</sup>	2001	Intervention
QUIST-PAULSEN et al <sup>445</sup>	2006	Intervention
RANSON et al <sup>446</sup>	2002	Comparators
RASCH et al <sup>447</sup>	2009	Other
RINGEN et al <sup>448</sup>	2002	Outcomes
RUGER et al <sup>449</sup>	2008	Intervention
SALIZE et al <sup>450</sup>	2009	Intervention
SCHAUFFLER et al <sup>451</sup>	2001	Study Design
SECKER-WALKER et al <sup>452</sup>	2005	Intervention
SINCLAIR et al <sup>453</sup>	1999	Intervention
SLATORE et al <sup>200</sup>	2009	Population
SMITH et al <sup>454</sup>	2007	Intervention
SOLBERG et al <sup>455</sup>	2006	Intervention
SONG et al <sup>456</sup>	2002	Other
STAPLETON et al <sup>457</sup>	1999	Comparators
STEVERMER <sup>458</sup>	1996	Other
STRIEBER <sup>459</sup>	1985	Other
SWANK et al <sup>460</sup>	1988	Comparators
TENGS et al <sup>461</sup>	2001	Intervention
THAVORN et al <sup>462</sup>	2008	Intervention
TILGREN et al <sup>463</sup>	1993	Intervention

<b>List of excluded economic studies</b>		
<b>Authors</b>	<b>Year</b>	<b>Reason for exclusion</b>
TOMSON et al <sup>464</sup>	2004	Intervention
TRAN et al <sup>465</sup>	2002	Intervention
TSEVAT <sup>466</sup>	1992	Study Design
VELICER et al <sup>467</sup>	1993	Intervention
VIJGEN et al <sup>468</sup>	2008	Intervention
WANG et al <sup>469</sup>	2008	Intervention
WANG et al <sup>470</sup>	2001	Intervention
WARNER et al <sup>471</sup>	1996	Intervention
WASEM et al <sup>472</sup>	2008	Comparators
WASLEY et al <sup>233</sup>	1997	Comparators
WELTON et al <sup>473</sup>	2008	Intervention

## APPENDIX 11: SELECTED REPORTS FOR ECONOMIC REVIEW



## APPENDIX 12: INCLUDED ECONOMIC STUDIES

<b>Included economic studies</b>	
<b>Akehurst and Piercy,<sup>214</sup> 1994</b>	
<b>Country, sponsorship, study design</b>	UK Not clear CEA
<b>Time horizon, study perspective, population</b>	36 years (years 1993 to 2029) UK National Health Service (NHS) Heavy smokers (those who smoke > 23 cigarettes/day); age 20+
<b>Interventions</b>	Nicotine (Nicorette) nasal spray (NNS) reimbursed under the treatment strategy of NNS + GP counselling
<b>Comparators</b>	Nicotine (Nicorette) nasal spray (NNS) as out-of-pocket (private prescription) + GP counselling
<b>Outcomes measured</b>	Net expenditure saved per life-year lost by not reimbursing NNS (= [savings by not reimbursing NNS - treatment costs incurred]/[Life years lost])
<b>Healthcare and other resources considered</b>	Cost of NNS Cost of GP counselling time (groups and individual) Costs incurred by NHS for treating ischemic heart disease (IHD) & lung cancer (LC)
<b>Quit rate [source]</b>	[Biochemically verified continuous abstinence at 12 months] NNS = 26% [one RCT]
<b>Relapse rate [source]</b>	0%
<b>Results</b>	Savings to NHS by not making NNS reimbursable = £116,681 to £149,531  Treatment costs of IHD & LC incurred = £73,529 to £151,922  Life years lost by not making NNS reimbursable = 49.0 to 101.3  Net expenditure savings/life-year lost without treatment costs of IHD & LC = £2,381 to £1,476  Net expenditure savings/life-year lost with treatment costs of IHD & LC = £881 to £-24 (i.e., treatment costs exceed savings from making NNS non-reimbursable)
<b>Conclusion</b>	Reimbursing NNS is cost-effective compared with the alternative of NNS being non-reimbursable
<b>Bertram et al.,<sup>202</sup> 2007</b>	
<b>Country, sponsorship, study design</b>	Australia None CUA
<b>Time horizon, study perspective, population</b>	Lifetime (until age of 100) Health system (government & patient) Current smokers, motivated to quit, age 20-79 years in Australia in 2000
<b>Interventions</b>	(1) Nicotine replacement therapy [Transdermal patches] (NRT; 6-12 weeks) + current practice (e.g. mass-media campaigns, tobacco taxation)

<b>Included economic studies</b>	
	(2) Bupropion (7 weeks) + current practice (3) NRT as a second-line treatment (when bupropion failed) + current practice
<b>Comparators</b>	Current practice
<b>Outcomes measured</b>	Cost per disability-adjusted life year (DALY) averted
<b>Healthcare and other resources considered</b>	Costs of NRT, bupropion Costs of doctor's visit (to receive prescription for bupropion) Treatment cost of smoking-related diseases
<b>Quit rate [source]</b>	[Continuous abstinence at 12 months, based on either biochemically verified or self report] Odds ratio (OR) for NRT (versus natural quit rate) = 1.73 (95% CI = 1.62-1.85) [meta-analysis] OR for bupropion (versus natural quit rate) = 2.54 (1.9-3.41) [meta-analysis] Natural quit rate = 8.6% (7.9 – 9.3) [meta-analysis]
<b>Relapse rate [source]</b>	Range: 10-48% (per year up to 4 years after the intervention) [4 studies]
<b>Results</b>	[per 1000 smokers] <u>NRT vs. current practice</u> # of additional quitters = 114; DALYs saved = 57 Total additional net cost (cost of intervention – potential cost saving due to reduced treatment cost of tobacco-attributed diseases; in millions) = A\$1.023 Incremental cost/DALY averted ≈ A\$17,000 <u>Bupropion vs. current practice</u> # of additional quitters = 148; DALYs saved = 74 Total additional net cost (cost of intervention – potential cost saving due to reduced treatment cost of tobacco-attributed diseases; in millions) = A\$0.59 Cost/DALY averted ≈ A\$7,900 (Cost/DALY averted was same regardless of NRT to be used as first- or second-line therapy)
<b>Conclusion</b>	Both NRT and bupropion are cost-effective relative to the current practice (with ICER far below the threshold of A\$42,000 per QALY and A\$33,000 per QALY specified by the authors)
<b>Bolin et al.,<sup>210</sup> 2006</b>	
<b>Country, sponsorship, study design</b>	Sweden GlaxoSmithKline, Sweden CUA
<b>Time horizon, study perspective, population</b>	20 years Societal and health care payer Smokers age ≥ 35 years old, reflecting Swedish population of 2001
<b>Interventions</b>	Bupropion + GP visit + motivational support (four visits)
<b>Comparators</b>	(1) Nicotine patches + GP visit + motivational support (two visits) (2) Nicotine gums + GP visit + motivational support (two visits)
<b>Outcomes measured</b>	Cost per quality-adjusted life year (QALY) gained
<b>Healthcare and other resources considered</b>	Intervention cost (utilization of health care personnel + drug cost) Diagnostic-specific inpatient care cost Physician visit, diagnostic-related drug prescriptions Indirect effects of reduced mortality (value of production minus value of

Included economic studies	
	consumption)
<b>Quit rate</b> [source]	[Continuous abstinence at 12 months, based on either biochemically verified or self report] Bupropion = 18.9% [meta-analysis] Nicotine patches = 15.6% [meta-analysis] Nicotine gums = 15.0% [meta-analysis]
<b>Relapse rate</b> [source]	2.1% per year [one study]
<b>Results</b>	<p>[per 612,7851 male and 780,970 female smokers]</p> <p><u>Bupropion vs. nicotine patches</u></p> <p>- With indirect effects (intervention + health care + indirect costs) [Male] Incremental cost <math>\approx</math> -95 million (Swedish kronas; SEK); QALY gained = 4,073 Bupropion dominating</p> <p>[Female] Incremental cost <math>\approx</math> -87 million (SEK); QALY gained = 5,201 Bupropion dominating</p> <p>- Without indirect effects (intervention + health care costs) [Male] Incremental cost <math>\approx</math> 27 million (SEK); QALY gained = 4,073 Incremental cost/QALY gained = 6,600 SEK</p> <p>[Female] Incremental cost <math>\approx</math> 25 million (SEK); QALY gained = 4,073 Incremental cost/QALY gained = 4,900 SEK</p> <p><u>Bupropion vs. nicotine gum</u></p> <p>- With indirect effects (intervention + health care + indirect costs) [Male] Incremental cost <math>\approx</math> -160 million (SEK); QALY gained = 4,814 Bupropion dominating</p> <p>[Female] Incremental cost <math>\approx</math> -162 million (SEK); QALY gained = 6,147 Bupropion dominating</p> <p>- Without indirect effects (intervention + health care costs) [Male] Incremental cost <math>\approx</math> -16 million (SEK); QALY gained = 4,814 Bupropion dominating</p> <p>[Female] Incremental cost <math>\approx</math> -30 million (SEK); QALY gained = 6,147 Bupropion dominating</p> <p><u>Nicotine patches vs. nicotine gum</u></p> <p>- With indirect effects (intervention + health care + indirect costs) [Male] Incremental cost <math>\approx</math> 255 million (SEK); QALY gained = 741 Incremental cost/QALY gained <math>\approx</math> 345,000 SEK</p> <p>[Female] Incremental cost <math>\approx</math> 250 million (SEK); QALY gained = 946 Incremental cost/QALY gained <math>\approx</math> 266,000 SEK</p> <p>- Without indirect effects (intervention + health care costs) Patch dominating for both males and females</p>

<b>Included economic studies</b>	
<b>Conclusion</b>	Bupropion dominates nicotine patches and gums in most cases Bupropion is cost-effective relative to nicotine gum (with ICER far below the specified threshold of 129,000 SEK to 333,000 SEK per QALY (in reference to a recently published study)
<b>Bolin et al,<sup>211</sup> 2008</b>	
<b>Country, sponsorship, study design</b>	Sweden Pfizer AB, Sweden CUA
<b>Time horizon, study perspective, population</b>	20, 50 and 80 (lifetime) years Societal and health care payer Smokers who attempt to quit (25% of all smokers in the Swedish population of 2003); age 18-100
<b>Interventions</b>	Varenicline (12 weeks; 1 mg, twice daily) + GP visit + Motivational support (2 visits)
<b>Comparators</b>	Bupropion (7 weeks; 150 mg, twice daily) + GP visit + Motivational support (4 visits)
<b>Outcomes measured</b>	Cost per quality adjusted life year (QALY) gained
<b>Healthcare and other resources considered</b>	Drug cost Cost of GP visit Cost of motivational support Morbidity-related health care cost of chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), stroke & lung cancer: (1) inpatient stays + outpatient visits, based on 3-year follow-up data of the county of Skane (which is comparable to data from Stockholm and Swedish National Board of Health and Welfare); (2) Prescribed drug cost for COPD and CHD, based on a representative survey of physicians in Sweden (drug costs for stroke and lung cancer were not available); (3) rehabilitation costs for stroke patients, based on a published study Indirect effects on production and consumption (values of production minus values of consumption, based on a published study)
<b>Quit rate [source]</b>	[Continuous abstinence at 12 months, based on biochemical verification] Varenicline = 22.5% Bupropion = 15.7% [2 head-to-head RCTs; pooled data]
<b>Relapse rate [source]</b>	Continuous abstinence between: 1 to 5 years = 6% per year 6 to 10 years = 2% per year 10+ years = 1% per year [each data is based on single published source]
<b>Results</b>	[per 168,844 male and 208,737 female smokers who attempt to quit smoking] <u>Varenicline vs. bupropion</u> With indirect effects (intervention + health care + indirect costs) (1) 20-year time horizon [Male] Incremental cost ≈ € 0.533 million; QALY gained = 2,591 Incremental cost/QALY gained = €2,056 [Female] Incremental cost ≈ €0.293 million; QALY gained = 2,455 Incremental cost/QALY gained = €1,193

<b>Included economic studies</b>	
	(2) 50-year time horizon [Male] Incremental cost $\approx$ €99.9 million; QALY gained = 6,776 Incremental cost/QALY gained = €14,743 [Female] Incremental cost $\approx$ €109.55 million; QALY gained = 7,707 Incremental cost/QALY gained = €14,214 Without indirect effects (intervention + health care costs) (1) 20-year time horizon [Male] Incremental cost $\approx$ € -7.74 million; QALY gained = 2,591 Varenicline dominating [Female] Incremental cost $\approx$ €-9.46 million; QALY gained = 2,455 Varenicline dominating (2) 50-year time horizon [Male] Incremental cost $\approx$ €-15.9 million; QALY gained = 6,776 Varenicline dominating [Female] Incremental cost $\approx$ €-24.0 million; QALY gained = 7,707 Varenicline dominating
<b>Conclusion</b>	When only health care costs were considered, varenicline was cost saving than bupropion When both health care costs, health care cost saving and indirect costs were considered, incremental cost per QALY gained was below the willingness to pay threshold specified by the authors (with reference to their previous study)
<b>Cornuz et al,<sup>225</sup> 2006</b>	
<b>Country, sponsorship, study design</b>	Canada, France, Spain, Switzerland, the United States, the United Kingdom None declared CEA
<b>Time horizon, study perspective, population</b>	Lifetime (until the age of 100 years) Third-party-payer Current smokers who smoked on average 20 cigarettes per day
<b>Interventions</b>	(1) Nicotine gum + GP counselling (2) Nicotine patch + GP counselling (3) Nicotine spray + GP counselling (except for Canada and France) (4) Nicotine inhaler + GP counselling (except for Canada and Spain) (5) Bupropion + GP counselling
<b>Comparators</b>	GP counselling only
<b>Outcomes measured</b>	Incremental cost per life-year saved
<b>Healthcare and other resources considered</b>	Time for GP counselling (initial cessation = 10 minutes), prescribing (15 minutes) and follow-up (five visits, each lasting for 15 minutes) [Canada: Ontario Medical Association, France: literature, Spain, the UK and the US: official government data, Switzerland: private medical data] Drug cost [Canada: survey of 50 selected retail pharmacies, the US: average pharmacotherapy prices from two nation-wide pharmacy chain, France, Spain,

<b>Included economic studies</b>	
	Switzerland and the UK: publicly or privately published price data]
<b>Quit rate [source]</b>	[Point prevalence at 1 year of abstinence (definition of point prevalence not clear)] Natural quit rate = 2.5% (95% CI: 1-4%) [published articles] Odds ratios (relative to no intervention) for counselling only = 1.73 (1.46-2.03) [two published meta-analyses] Odds ratios (relative to counselling only) for nicotine replacement therapy (NRT): Nicotine gum = 1.66 (1.52-1.82); Nicotine patch = 1.80 (1.61-2.01); Nicotine spray = 2.35 (1.63-3.38); Nicotine inhaler = 2.14 (1.44-3.18) [two published meta-analyses] Odds ratios (relative to counselling only) for bupropion = 2.51 (1.50-3.00) [a published meta-analysis]
<b>Relapse rate [source]</b>	Lifetime probability of relapse after 1 year of cessation = 35% [2 published articles]
<b>Results</b>	Comparison with counselling only (for various age groups): Nicotine gum: [Male] Incremental cost-effectiveness ratio (ICER) = €4266 (age 45-49) to €6879 (age 65-69); [Female] ICER = €5178 (age 50-54) to €8799 (age 25-29) Nicotine patch: [Male] ICER = €3113 (age 45-49) to €5021 (age 65-69); [Female] ICER = €3779 (age 50-54) to €6423 (age 25-29) Nicotine spray: [Male] ICER = €3669 (age 45-49) to €5918 (age 65-69); [Female] ICER = €4454 (age 50-54) to €7570 (age 25-29) Nicotine inhaler: [Male] ICER = €3700 (age 45-49) to €5968 (age 65-69); [Female] ICER = €4537 (age 55-59) to €7634 (age 25-29) Bupropion: [Male] ICER = €1768 (age 45-49) to €2851 (age 65-69); [Female] ICER = €2146 (age 50-54) to €3646 (age 25-29)
<b>Conclusion</b>	Bupropion and nicotine patch were more cost-effective interventions than nicotine gum, spray and inhaler Cost-effectiveness of NRT and bupropion varies widely with age and sex
<b>Feenstra et al,<sup>205</sup> 2005</b>	
<b>Country Sponsorship Study design</b>	The Netherlands Dutch Public-Private Partnership to reduce tobacco dependence CEA, CUA
<b>Time horizon, study perspective, population</b>	75 years Societal (but productivity costs were not included) Dutch population of smokers aged 10 years and older
<b>Interventions</b>	(1) Telephone counselling (one 30-minute call + 6 follow-up call (lasting 15 minutes each) based on questionnaire completed by the potential quitters [TC] (2) Minimal counselling (by a GP and/or a GP assistant in one or two consultations with a total length of 12 minutes) [MC] (3) Minimal GP counselling + 8-week nicotine patches or gum (NRT) [MC+NRT] (4) Intensive counselling (by a trained lung nurse for a total of 90 minutes + a 2-minute stop advice from a lung physician) + 12-week NRT [IC+NRT] (5) Intensive counselling (by a trained lung nurse + a 2-minute stop advice by a lung specialist) + 9-week bupropion [IC+BUP]
<b>Comparators</b>	Current practice (the mix of all current smoking cessation initiatives in the Netherlands; the combination of MC, MC+NRT, IC+NRT, IC+BUP, TC and will power alone) [CP]
<b>Outcomes</b>	Costs per additional quitter, costs (including or excluding savings of treatment for

<b>Included economic studies</b>	
<b>measured</b>	diseases) per LY or QALY gained
<b>Healthcare and other resources considered</b> [source]	Counsellor time, GP time, self-help manuals, NRT prescription, chest physician time, lung nurse time and BUP prescription [Dutch empirical data and the Dutch Foundation for Pharmaceutical Statistics]
<b>Quit rate</b> [source]	[12 month prolonged abstinence rates, based on either biochemically verified or self report]  CP (average across all age groups and sexes) = 3.4% (range: 0.007 for men & women aged 10 to 14 years, 0.049 for men aged 60+ and 0.051 for women aged 70+) [STIVORO annual population monitoring studies & three cohort studies] TC* = 7.6 % (95% CI: 6.9-8.3) (for all age-sex groups) [2 meta-analysis (9 RCTs) & 1 evaluation study] MC* = 7.9 (4.7-11.1) (for all age-sex groups) [1 RCT] MC + NRT* = 12.7 (11.9-13.5) [2 meta-analysis (17 RCTs)] IC + NRT* = 15.1 (14.1-16.1) [2 meta-analysis (26 RCTs)] IC + BUP* = 17.2 (14.0-20.4) [2 meta-analysis (4 RCTs)] *Age- and sex-specific quit rates for each intervention was calculated as: [(Quit rate for all age-sex groups)/(Average quit rate of CP (3.4%))] * [Age-sex specific quit rate for CP]
<b>Relapse rate</b> [source]	Varies by age and sex: maximum rate = 0.099 (for men aged 40-44), 0.114 (for women aged 40-44); relapse rate was assumed to be 0 for men > 74 years & women > 70 years [STIVORO annual population monitoring studies]
<b>Results</b>	Selected results (compared with CP; initial cohort size of 1,000 smokers): [Cost per quitter] (1) IC+NRT: €2,970/quitter (117 additional quitter, €348,000 additional costs); (2) IC+BUP: €2,410/quitter (138 additional quitter, €333,000 additional costs) [Cost per QALY gained, 1-year implementation of intervention] (1) IC+NRT: €5,200/QALY gained (45,000 additional QALY, €240 million additional costs); (2) IC+BUP: €3,600/QALY gained (53,000 additional QALY, €200 million additional costs) [Cost per QALY gained, permanent implementation of intervention] (1) IC+NRT: €4,900/QALY gained (940,000 additional QALY, €4.6 billion additional costs); (2) IC+BUP: €3,400/QALY gained (1.1 million additional QALY, €3.7 billion additional costs)
<b>Conclusion</b>	(1) MC was cost saving compared with CP, (2) ICER (compared with CP) for MC+NRT, IC+NRT, IC+BUP and TC were small, ranging from €1,100/QALY gained (TC) to €4,900/QALY gained (IC+NRT), (3) Costs per LY gained of IC+BUP were more favourable than those of IC+NRT
<b>Flack et al,<sup>215</sup> 2007</b>	
<b>Country, sponsorship, study design</b>	UK Not clear CUA
<b>Time horizon, study perspective,</b>	Lifetime Workplace, UK National Health Service A cohort of adult (age 16+) smokers in the UK general population

<b>Included economic studies</b>	
<b>population</b>	
<b>Interventions</b>	(1) Brief advice (3 minutes with GP) [BA] (2) BA (4 minutes with GP) + self-help material [BA+SELF] (3) BA (7 minutes with GP) + SELF + nicotine replacement therapy [BA+SELF+NRT] (4) BA (4 minutes with GP) + SELF + NRT (60 patches) + specialist clinic [BA+SELF+NRT+CLINIC] (5) BUP (8 weeks) + less intensive counselling (5-10 minute scripted call) [BUP+LIC] (6) BUP (8 weeks) + more intensive counselling (5 calls with smoking specialist) [BUP+MIC] (7) Nicotine patch (5 weeks) [NP] (8) NP (5 weeks) + group counselling (5 group visits) [NP + GC] (9) NP (5 weeks) + individual counselling (5 clinic visits) [NP + IC] (10) NP (5 weeks) + pharmacist consultation (5 pharmacist consultations) [NP + PC] (11) NP (5 weeks) + pharmacist consultation + behavioural program (5 behavioural clinic visits) [NP + PCBP]
<b>Comparators</b>	No intervention [NOTREAT]
<b>Outcomes measured</b>	Costs per QALY gained
<b>Healthcare and other resources considered</b>	Costs associated with co-morbidity [UK National Audit Office, British Heart Foundation, UK department of health, previous UK cost study, National Health Service, NICE guideline]; Intervention costs [previous UK cost study, British National Formulary]
<b>Quit rate [source]</b>	[12-month abstinence, the definition of abstinence is not clear] (1) BA = 3% (2) BA+SELF = 4% (3) BA+SELF+NRT = 6% (4) BA+SELF+NRT+CLINIC = 15% (5) BUP+LIC = 24% (6) BUP+MIC = 31% (7) NP = 12% (8) NP + GC = 21% (9) NP + IC = 16% (10) NP + PC = 24% (11) NP + PCBP = 35% (12) Background cessation rate = 2% (Source: previous economic evaluation studies)
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	<u>Compared with NOTREAT</u> (1) All the intervention (except for BA+SELF+NRT) dominated NOTREAT (incremental cost: between -£12 and -£414; incremental QALY: between 0.01 and 0.30) (2) BA+SELF+NRT versus NOTREAT: ICER = £984 (incremental cost = £36, incremental QALY = 0.04) <u>Compared with BA</u>

<b>Included economic studies</b>	
	(1) All the intervention (except for BA+SELF+NRT) dominated BA (incremental cost: between -£15 and -£402; incremental QALY: between 0.01 and 0.29) (2) BA+SELF+NRT versus NOTREAT: ICER = £1,768 (incremental cost = £48, incremental QALY = 0.03)
<b>Conclusion</b>	(1) All interventions considered were cost-effective when compared with the NOTREAT strategy (2) MIC+BUP cost the least and was the most effective intervention
<b>Gilbert et al,<sup>208</sup> 2004</b>	
<b>Country, sponsorship, study design</b>	The Seychelles Not stated CEA
<b>Time horizon, study perspective, population</b>	Lifetime Payer (Ministry of Health) Smokers aged 20 years and older in Seychelles
<b>Interventions</b>	(1) Nicotine gum (3 months) + physician counselling (10-minute session and six 15-minute follow-up sessions (follow-up sessions are only to those who receive pharmacotherapy) [GUM+COUNSEL] (2) Nicotine patch (3 months) + COUNSEL [PATCH+COUNSEL] (3) Nicotine spray (3 months) + COUNSEL [SPRAY+COUNSEL] (4) Nicotine inhaler (3 months)+ COUNSEL [IHNALER+COUNSEL] (5) Bupropion (3 months) + COUNSEL [BUP+COUNSEL]
<b>Comparators</b>	COUNSEL only
<b>Outcomes measured</b>	Cost per life-year saved
<b>Healthcare and other resources considered</b>	Drug costs [US retail prices], health care providers' costs [National Health Service wage]
<b>Quit rate [source]</b>	[12-month continuous cessation, based on either biochemically verified or self report] Natural quit rate = 2.5% [previous studies] COUNSEL = Odds ratio (OR) (vs. no intervention) = 1.73 GUM = OR (vs. counselling only) = 1.66 PATCH = OR (vs. counselling only) = 1.80 SPRAY = OR (vs. counselling only) = 2.35 INHALER = OR (vs. counselling only) = 2.14 BUP = OR (vs. counselling only) = 2.51 *Data source: two meta-analyses and one guideline (except for natural quit rate)
<b>Relapse rate [source]</b>	Lifetime relapse rate after 1 year of abstinence = 35% [previous studies]
<b>Results</b>	(Age at intervention between 20-64 years old with 15-year age groups, reference = COUNSEL only) Male GUM+COUNSEL (vs. COUNSEL) = US\$3,675 to US\$4,870/life-year saved PATCH+COUNSEL = US\$1,962 to US\$2,600/life-year saved SPRAY+COUNSEL = US\$4,551 to US\$6,032/life-year saved INHALER+COUNSEL = US\$4,248 to US\$5,630/life-year saved BUP+COUNSEL = US\$1,311 to US\$1,738/life-year saved Female

<b>Included economic studies</b>	
	GUM+COUNSEL (vs. COUNSEL) = US\$5,753 to US\$7,894/life-year saved PATCH+COUNSEL = US\$3,071 to US\$4,214/life-year saved SPRAY+COUNSEL=US\$7,124 to US\$9,777/life-year saved INHALER+COUNSEL=US\$6,650 to US\$9,125/life-year saved BUP+COUNSEL=US\$2,052 to US\$2,817/life-year saved
<b>Conclusion</b>	Pharmacological smoking cessation intervention, particularly BUP, PATCH and GUM, in combination with COUNSEL can be highly cost-effective as compared to other medical interventions in low mortality, middle-income countries
<b>Hall et al,<sup>216</sup> 2005</b>	
<b>Country, sponsorship, study design</b>	USA Grant information was provided with no clear details CEA
<b>Time horizon, study perspective, population</b>	52 weeks Health care payer Community volunteers of 220 cigarette smokers from the San Francisco Bay area (in 1997 to 1999) who wanted to quit smoking and willing to participate in a clinical trial to test efficacy of nortriptyline, bupropion, and psychological intervention for smoking cessation.
<b>Interventions</b>	[treatment took place during weeks 1 to 12] (1) Medical management (MM: brief advice from physician at weeks 1, 2, 6 and 11) + Psychological intervention (PI: 5 group sessions (of group size of 3 to 11) with counsellors + Placebo (PL) [MM+PI+PL] (2) MM + nortriptyline (NORT: for 12 weeks) [MM+NORT] (3) MM + bupropion (BUP: 150 mg/day for the first 3 days, 300 mg/day from day 4 to week 12) [MM+BUP]
<b>Comparators</b>	MM + PL
<b>Outcomes measured</b>	Cost per additional quitter
<b>Healthcare and other resources considered</b>	Drug cost [Drug Topics Red Book], blood draw/assay (nortriptyline only), physician time [National Compensation Survey], counsellor time [based on costs occurred during the clinical study], space rental [based on the monthly rent per square foot at the trial site], written materials [based on publisher's price or the cost of duplication], electrocardiograph cost (nortriptyline only)
<b>Quit rate [source]</b>	[Biochemically verified 7-day point prevalence abstinence rates at week 52] MM+PL = 13% MM+PI+PL = 21% MM+NORT = 23% MM+BUP = 29% [all based on 1 RCT conducted by the study authors]
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	(1) MM+PI+PL vs. MM+PL: \$440/quitter (8% additional quitters, \$35 additional costs), (2) MM+NORT vs. MM+PL: \$741/quitter (10% additional quitters, \$79 additional costs), (3) MM+BUP vs. MM+PL: \$1,509/quitter (16% additional quitters, \$237 additional costs)
<b>Conclusion</b>	MM+NORT was more cost-effective than MM+BUP, and MM+PI+PL was more cost-effective than MM+NORT or MM+BUP. However, differences in cost-

<b>Included economic studies</b>	
	effectiveness among these alternatives were not statistically significant
<b>Halpern et al,<sup>223</sup> 2000</b>	
<b>Country, sponsorship, study design</b>	USA Glaxo Wellcome Inc. CBA
<b>Time horizon, study perspective, population</b>	Time until retirement (at age 65) Not explicitly stated but implied as health plans and employers Employees or health plan members and their adult dependents aged 18 and older in the US
<b>Interventions</b>	Costs to acquire bupropion (i.e., drug cost, physician visits to receive bupropion prescriptions and time off from work for physician visits) in interventions below are subject to reimbursement: (1) Bupropion (9 weeks, 150mg twice daily)+minimal counselling [BUP+MCOUNSEL] (2) BUP+brief counselling [BUP+BCOUNSEL] (3) BUP+full counselling [BUP+FCOUNSEL] (4) BUP + nicotine patch + MCOUNSEL [BUP+PATCH+MCOUNSEL], (5) BUP + PATCH + BCOUNSEL, (6) BUP+PATCH+FCOUNSEL (7) PATCH+MCOUNSEL, (8) PATCH+BCOUNSEL (9) PATCH+FCLUNSEL (10) MCOUNSEL only (11) BCOUNSEL only (12) FCOUNSEL only
<b>Comparators</b>	Costs to acquire bupropion are not subject to reimbursement
<b>Outcomes measured</b>	Benefit-to-cost ratio (Incremental health care costs saved by covering cessation intervention divided by incremental dollar spent on cessation intervention)
<b>Healthcare and other resources considered</b>	Intervention costs (drug and counselling costs) [average wholesale price, literature review], health care costs (costs for acute and chronic conditions) [a previous study] Costs for increased absenteeism and decreased productivity, employees' time off from work to receive treatment [previous literatures]
<b>Quit rate [source]</b>	[Definition of quit rates not provided] (1) BUP+MCOUNSEL = 13.7% (2) BUP+BCOUNSEL = 15.4% (3) BUP+FCOUNSEL = 23.0% (4) BUP+PATCH+MCOUNSEL = 18.9% (5) BUP + PATCH + BCOUNSEL = 20.6% (6) BUP+PATCH+FCOUNSEL = 28.2% (7) PATCH+MCOUNSEL = 7.7% (8) PATCH+BCOUNSEL = 9.4% (9) PATCH+FCLUNSEL = 17.0% (10) MCOUNSEL only = 1.3% (11) BCOUNSEL only = 3.2% (12) FCOUNSEL only = 7.5% *Source: previous studies
<b>Relapse rate</b>	Considered (based on the number of years since cessation; values not stated in

<b>Included economic studies</b>	
<b>[source]</b>	text) [1990 US Surgeon General's report]
<b>Results</b>	[For managed care organization setting for various areas of US (West, Northeast, Midwest and South)] Benefit-to-cost ratios comparing costs with and without smoking cessation cost reimbursement: US\$4.10 to US\$4.69 (i.e. for every dollar the managed care organization spent on cessation program, US\$4.10 to US\$4.69 in health care costs was saved) [For Health Plans setting for various areas of US (West, Northeast, Midwest and South)] Benefit-to-cost ratios comparing costs with and without smoking cessation cost reimbursement: US\$5.04 to US\$6.48
<b>Conclusion</b>	Coverage of BUP is cost savings for health plans and employers
<b>Halpern et al,<sup>217</sup> 2007</b>	
<b>Country, sponsorship, study design</b>	USA Pfizer CEA
<b>Time horizon, study perspective, population</b>	2, 5 and 10 years Private health plans, Medicaid plans or employees Adult US population (aged 18 and older) who are employed, with private health plan or with Medicaid in 2003
<b>Interventions</b>	Varenicline (12 weeks) + low-to moderate counselling (10-minutes with a clinician) [VAL]
<b>Comparators</b>	(1) Bupropion (12 weeks) + low to moderate counselling (10 minutes with a clinician) [BUP+COUNSEL] (2) Nicotine patches (9 weeks) + weekly counselling sessions [NRT+COUNSEL] (3) Counselling only (a 10-minute counselling session) [COUNSEL]
<b>Outcomes measured</b>	Cost per additional quitter
<b>Healthcare and other resources considered</b>	Drug cost [Red book with 80% of the average wholesale prices], counselling cost [applying costs for moderate counselling sessions for all treatment; Medicare national allowable average reimbursement], medical care costs [an empirical study of healthcare costs by smoking status]  Workplace cost (absenteeism and productivity losses, for employee perspective only) [a prospective study]
<b>Quit rate [source]</b>	[Biochemically verified continuous abstinence rates at 12 month] VAL+COUNSEL = 22.5% [2 head to head RCTs with bupropion] BUP+COUNSEL = 15.5% [2 head to head RCTs with varenicline] NRT+COUNSEL = 9.8% [1 head to head RTC with bupropion] COUNSEL = 3.2% [previous economic study]
<b>Relapse rate [source]</b>	14% at year two (since quitting), 10.5% at year three 3.4% at year four, 3.0% at year five, 1.5% at years six to 11, 0.0% at years >11 [1990 Surgeon General's Report on Smoking and Health]
<b>Results</b>	Selected results (2 year time horizon) [Employee perspective (excluding absenteeism and productivity; when these indirect costs were included, VAL became more cost-effective against all the comparators)] (1) VAL vs. BUP: VAL is more cost-effective,

<b>Included economic studies</b>	
	(2) VAL vs. NRT: \$129/additional quitter, (3) VAL vs. NOAID: \$756.20/additional quitter [Private Health Plan perspective] (1) VAL vs. BUP: VAL is more cost-effective, (2) VAL vs. NRT: \$20.74/additional quitter, (3) VAL vs. NOAID: \$648.06/additional quitter [Medicaid perspective] (1) VAL vs. BUP: VAL is more cost-effective, (2) VAL vs. NRT: VAL is more cost-effective, (3) VAL vs. NOAID: \$835.80/additional quitter *Disaggregated data for incremental costs and effects separately are not shown due to lack of information
<b>Conclusion</b>	(1) VAL is cost saving within 2 to 5 years compared with NRT (patches) or NOAID. (2) VAL provides reduced cessation costs and decreased health care costs compared with BUP (3) Results are consistent across different study perspectives (4) When indirect costs (productivity and absenteeism) are included, VAL became cost saving to employers within its first year of use
<b>Heitjan et al,<sup>222</sup> 2008</b>	
<b>Country, sponsorship, study design</b>	USA National Cancer Institute and National Institute on Drug Abuse CEA
<b>Time horizon, study perspective, population</b>	Lifetime Not clear Current smokers aged between 20 and 60 years
<b>Interventions</b>	(1) Treating all individuals with Nicotine Replacement Therapy (8 weeks) + counselling [NRT+COUNSEL] (2) Treating all individuals with bupropion (10 weeks) + COUNSEL [BUP+COUNSEL] (3) A genetically tailored plan (genetic tests) to choose between NRT+COUNSEL or BUP+COUNSEL strategy [TEST] (4) Treating all individuals with varenicline (12 weeks) [VAL] + COUNSEL [VAL+COUNSEL]
<b>Comparators</b>	No treatment [NOTREAT]
<b>Outcomes measured</b>	Cost per life-year gained
<b>Healthcare and other resources considered</b>	Treatment costs (genetic testing [manufacture], smoking cessation counselling [based on the author's institution], drugs [pharmacy database])
<b>Quit rate [source]</b>	[Annual quit rate (definition not clear), based on biochemical verification or self report] NOTREAT = 5% [literature review], BUP (with CC homozygotic genotype) = 27% [2 RCTs], BUP (with either CC homozygotic or NN homozygotic genotype)= 17% [2 RCTs] NRT = (with CC homozygotic genotype) = 19% [2 RCTs] BUP (with either CC homozygotic or NN homozygotic genotype)= 23% [2 RCTs] VAL = 35% [a meta-analysis and 2 RCTs]

<b>Included economic studies</b>	
	Permanent quit rate = 60% (a probability that one quit permanently after a treatment) [a previous study]
<b>Relapse rate [source]</b>	Annual relapse rate = 50% (for those who do not quit permanently) [a previous study]
<b>Results</b>	(1) NRT+COUNSEL vs. BUP+COUNSEL: BUP+COUNSEL is significantly more effective and costs less (2) TEST vs. BUP+COUNSEL: BUP+COUNSEL is equally effective (in terms of statistical significance) and costs less (3) BUP+COUNSEL vs. NOTREAT: US\$1,557/life-year gained (Additional cost (BUP-NOTREAT) = US\$1,031, additional life-years = 0.66) (4) VAL+COUNSEL vs. BUP+COUNSEL: US\$2,985/life-year gain (Additional cost = US\$428, additional life-year gain = 0.14)
<b>Conclusion</b>	(1) Untailored VAL was the most effective and expensive treatment among treatment strategies considered, (2) Untailored smoking cessation interventions with either VAL or BUP are cost-effective
<b>Hill,<sup>218</sup> 2006</b>	
<b>Country, sponsorship, study design</b>	USA None declared CEA
<b>Time horizon, study perspective, population</b>	6 month Texas government General population in Texas
<b>Interventions</b>	(1) NRT gum (48mg/day) [GUM] (2) Zyban (300mg/day) [ZYBAN] (3) Zyban (300mg/day)+ NRT gum (48mg/day) [ZYBAN+GUM] (4) NRT patch (14mg/day) [PATCH] (5) NRT gum (48mg/day) + NRT patch (14mg/day) [GUM+PATCH] (6) NRT inhaler (12 units/day) [INHALER] (7) Zyban (300mg/day) + NRT patch (21mg/day) [ZYBAN+PATCH] (8) NRT nasal spray (24 sprays/day) [SPRAY] (9) Nortriptyline (50mg/day) [NORT] (10) Clonidine (0.2mg/day) [CLON] *Length of intervention: 8 weeks, all interventions include 6-minute physician counselling for advice and dissemination for prescription
<b>Comparators</b>	None specified
<b>Outcomes measured</b>	Cost per additional quitter
<b>Healthcare and other resources considered</b>	Drug cost and dispensing fees [Drug Topics Red Book], physician time [Texas Medicare reimbursement rates]
<b>Quit rate [source]</b>	[Continuous abstinence at 6 months; based on either biochemically verified or self report] GUM = 0.237, ZYBAN = 0.305, ZYBAN+GUM = 0.330 [assumed to be the same as ZYBAN+PATCH efficacy], PATCH = 0.177, GUM+PATCH = 0.286,

<b>Included economic studies</b>	
	INHALER = 0.228, ZYBAN+PATCH = 0.330 [1 RCT], SPRAY = 0.305 *Source for all the efficacy estimates: Surgeon General's Report 1996 (otherwise indicated)[This 1996 report is no longer available but the updated version is available through: <a href="http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf">http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf</a>
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	[All the comparisons are with respect to GUM] (1) ZYBAN: \$2,251/additional quitter (Cost (ZYBAN - GUM) = \$153.1, Additional % quit = 0.068), (2) ZYBAN+GUM: \$2,466/additional quitter (Cost (ZYBAN+GUM - GUM) = 61.7, Additional % quit = 0.025), (3) PATCH: dominated by GUM (i.e. GUM costs less and more effective), (4) GUM+PATCH: dominated by GUM, (5) INHALER: dominated by GUM, (6) ZYBAN+PATCH: dominated by GUM, (7) SPRAY: dominated by GUM
<b>Conclusion</b>	Among pharmacological interventions approved for the general population, GUM is the most cost-effective strategy. Therefore, GUM may be the best candidate for a state-wide implementation of smoking-cessation program for general population of smokers attempting to quit smoking
<b>Hoogendoorn et al,<sup>206</sup> 2008</b>	
<b>Country, sponsorship, study design</b>	the Netherlands Pfizer Inc. CUA
<b>Time horizon, study perspective, population</b>	Lifetime (until 100 years old) Dutch healthcare Population of Dutch smokers aged 18 and older
<b>Interventions</b>	Varenicline [VAL] *Length of intervention: 12 weeks, all pharmacological strategies (both intervention and comparators) include 120-minute counselling and 5-minute GP consultation time for prescribing the medication
<b>Comparators</b>	(1) Bupropion [BUP], (2) Nortriptyline [NORT], (3) Nicotine replacement therapy (patch or gum) [NRT], (4) Placebo [PL], (5) Unaided cessation [NOAID]
<b>Outcomes measured</b>	Cost per additional quitter, Cost per LY gain, Cost per QALY gain
<b>Healthcare and other resources considered</b>	Drug cost (NRT costs were calculated as weighted average of gum and patches) [Dutch Healthcare Insurance Board], counselling and GP consultation time for prescribing the medication [one previous Dutch study], health care costs of chronic conditions [various previous Dutch studies]
<b>Quit rate [source]</b>	[12-months continuous abstinence, based on either biochemically verified or self report] VAL = 22.4% [2 RCTs]

<b>Included economic studies</b>	
	BUP = 17.0% [a meta-analysis of 17 studies] NORT = 15.4% [a meta-analysis of 3 studies], NRT = 14.8% [a meta-analysis of 47 studies], PL = 9.3% [2 RCTs (same as those for VAL)], NOAID = 5.0% [a previous review paper]
<b>Relapse rate [source]</b>	6.8% between 1-5 years after a successful quit (12-month continuous abstinence) [a previous Dutch study], 0% after 5 years [assumed]
<b>Results</b>	[Selected results: Cohort of 884,000 smokers making a quit attempt, compared with VAL] Cost per LY gained (= [additional intervention costs-savings from prevented disease]/[LY gained]) (1) BUP: VAL cost saving (€ - 44million (VAL - BUP); 24,800 LY gain) (2) NORT: €2,510/LY gained (€80.8million; 32,100 LY gain) (3) NRT: VAL cost saving (€ - 78.4million; 35,000 LY gain) Cost per QALY gained (= [additional intervention costs-savings from prevented disease]/[QALY gained]) (1) BUP: VAL cost saving (€ - 44million; 37,800 QALY gain) (2) NORT: €1,650/QALY gained (€80.8million; 49,000 QALY gain) (3) NRT: VAL cost saving (€ - 78.4million; 53,500 QALY gain) *Compared with NOAID, NORT is cost-saving in terms of costs per LY and QALY gained; Incremental cost-effective ratios for other comparisons are between €320 to €2,630 per LY or QALY gained
<b>Conclusion</b>	(1) VAL is cost-effective compared with NORT and NOAID interventions (2) VAL is cost-saving compared with BUP and NRT
<b>Howard et al,<sup>219</sup> 2008</b>	
<b>Country, sponsorship, study design</b>	USA Pfizer Inc. CUA
<b>Time horizon, study perspective, population</b>	Lifetime (until 100 years old) and 20 years US health care system Adult smokers (aged 18 and older) in the US representing the 2004 US population
<b>Interventions</b>	Varenicline (1mg twice daily for 12 weeks) [VAL]
<b>Comparators</b>	(1) Bupropion (150mg/day for the first 3 days, followed by 150mg twice daily for 12 weeks) [BUP], (2) Nicotine replacement therapy (Gum, inhaled (inhaler and nasal spray) or patch for 12 weeks) [NRT], (3) Unaided cessation [NOAID]
<b>Outcomes measured</b>	Cost per QALY gain
<b>Healthcare and other resources considered</b>	Drug costs [US Red Book] (costs of NRT are weighted average of gum, inhaled and patch), physician visit (for VAL, BUP and NRT inhaled), morbidity-related costs [previous studies]
<b>Quit rate [source]</b>	[52-week continuous abstinence, based on either biochemically verified or self report] VAL = 22.4%, BUP = 15.4%, PL = 9.3%, NRT = 15.4% [a meta-analysis of 105 studies],

<b>Included economic studies</b>	
	NOAID = 5% [a previous review study] *Quit rates for VAL, BUP and PL were from pooled data of two head-to-head RCTs
<b>Relapse rate [source]</b>	6.3% for years 2 to 5 after the intervention [a previous longitudinal study], 2% for years 6 to 10 [Veteran's Affairs normative aging study], 1% for years 11+ [Veteran's Affairs normative aging study]
<b>Results</b>	[Cohort size of 11,925,455 US adult smokers who are making quit attempt] VAL is more effective and less expensive compared with any other options considered: Cost (in \$US million): VAL = 328,541, BUP = 330,958, NRT = 332,662, NOAID = 333,283 QALY (in 1,000): VAL = 174,346, BUP = 173,972, NRT = 173,970, NOAID = 173,416
<b>Conclusion</b>	VAL was more effective and was less expensive than all other smoking cessation interventions considered in the study. VAL is likely to be a cost-effective intervention compared with currently available alternatives in the US.
<b>Igarashi et al,<sup>204</sup> 2009</b>	
<b>Country, sponsorship, study design</b>	Japan Pfizer Japan Inc. CUA
<b>Time horizon, study perspective, population</b>	Lifetime (until the age of 90 years) (5-year Markov cycle) Healthcare payer Smokers who started smoking at the age of 20 years
<b>Interventions</b>	Varenicline + physician counselling (12 weeks) [VAL+COUNSEL]
<b>Comparators</b>	Placebo + COUNSEL (12 weeks) [PL+COUNSEL]
<b>Outcomes measured</b>	Cost per QALY gained
<b>Healthcare and other resources considered</b>	Treatment costs of smoking-related diseases [Patient Survey and survey of medical care activities in public health insurance in Japan], drug cost [National Health Insurance Drug Tariff], other intervention costs (e.g. administration, visit fee) [National Tariff of Medical Fees]
<b>Quit rate [source]</b>	[12-month continuous abstinence, biochemically verified] Male smokers VAL+COUNSEL = 37.9%, PL+COUNSEL = 25.5% Female smokers VAL+COUNSEL = 22.2%, PL+COUNSEL = 16.1% *Data source: 1 RCT
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	<u>Total smoker (Male+Female)</u> Lifetime costs of VAL+COUNSEL is lower and QALY is greater compared with PL+COUNSEL (i.e. VAL+COUNSEL is a dominant strategy)  <u>Male</u> For all male smokers and for each age at intervention, VAL+COUNSEL is a dominant strategy  <u>Female</u> For all female smokers and for each age at intervention, ICER range between US\$5,225/QALY gain and US\$1,503/QALY gain

<b>Included economic studies</b>	
<b>Conclusion</b>	VAL appears to be cost-effective and may contribute future cost savings in Japan.
<b>Jackson et al,<sup>220</sup> 2007</b>	
<b>Country, sponsorship, study design</b>	USA Pfizer Inc. CBA
<b>Time horizon, study perspective, population</b>	1 year Employer US employers and employees
<b>Interventions</b>	Varenicline (12 weeks: 0.5mg/day for days 1-3; 0.5mg twice daily for days 4-7, 1mg twice daily thereafter) + Brief individual counselling ( ≤ 10 minutes each visit, 16 visits) [VAL+COUNSEL]
<b>Comparators</b>	(1) Bupropion (12 weeks: 150mg/day for days + placebo for the second dose, 150mg twice daily thereafter) (both brand and generic were considered)+ COUNSEL [BUP+COUNSL] (2) Placebo (12 weeks: twice daily)+ COUNSEL [PL+COUNSEL]
<b>Outcomes measured</b>	Net benefit of treatment [Monetary benefit (saving) to employer to produce a non-smoking employee - Cost of intervention]
<b>Healthcare and other resources considered</b>	Drug cost [Wholesale acquisition costs], counselling cost [assumed], physician consultation cost [Current procedural terminology (CPT) codes] Cost [or cost savings] to the employer for an employee who smokes [quit smoking] (absenteeism, medical care, non-health related insurance (e.g. workers' compensation, accidental injury, fire insurance), on-job time) [previous studies]
<b>Quit rate [source]</b>	[Biochemically verified continuous abstinence for weeks 9 through 52] VAL = 21.9%, BUP = 16.1%, PL = 8.4% [all based on one RCT]
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	[Net benefit to the employer for the first year that an employee does not smoke (based on annual cost to an employer of US\$5,390/employee who smokes)] (1) VAL+COUNSEL = US\$540.6 (2) BUP (generic)+COUNSEL (generic) = US\$269.8 (3) BUP (brand name)+COUNSEL = US\$150.8 (4) PL+COUNSEL = US\$81.8
<b>Conclusion</b>	VAL provides the greatest net benefit to the employer at 1 year after the intervention.
<b>Kaper et al,<sup>207</sup> 2006</b>	
<b>Country, sponsorship, study design</b>	The Netherlands STIVORO and the Dutch Asthma Foundation CEA, CUA
<b>Time horizon, study perspective, population</b>	12 months and lifetime Societal General population of smokers aged 18 and older in the Netherlands
<b>Interventions</b>	
<b>Comparators</b>	No information about reimbursement [CONTROL]

<b>Included economic studies</b>	
<b>Outcomes measured</b>	Cost per additional quitter, cost per QALY gain
<b>Healthcare and other resources considered</b>	Intervention costs (overhead costs [RCT study], drug costs [manufacturer], counselling cost [standard rates (source unclear)]), Travel costs, costs due to lost productivity [previous studies]
<b>Quit rate [source]</b>	[7-day point abstinence at 6 months, biochemically verified] REIMBURSE = 7.8%, CONTROL = 5.5% [1 RCT] [7-day point abstinence at 12 month and no smoking between the 6-month and 12-month assessment periods] REIMBURSE = 5.5%, CONTROL = 2.8% [1 RCT]
<b>Relapse rate [source]</b>	Lifetime relapse rate after 1 year of abstinence = 35% [a previous study]
<b>Results</b>	[Time horizon = 12 months] REIMBURSE vs. CONTROL: €1,148/additional quitter (Additional cost (REIMBURSE - CONTROL) = €31, additional quitter = 2.7%) [Time horizon = lifetime] REIMBURSE vs. CONTROL: €1,802/QALY gain (Additional cost = €31, additional QALY ≈ 0.016)
<b>Conclusion</b>	Reimbursement for smoking cessation interventions seems to be cost-effective if Dutch society is willing to pay €10,000 per quitter or €18,000 per QALY gain (based on probabilistic analyses)
<b>McGhan and Smith,<sup>224</sup> 1996</b>	
<b>Country, sponsorship, study design</b>	USA Lederle Laboratories CBA
<b>Time horizon, study perspective, population</b>	1 year Employer US employers and employees
<b>Interventions</b>	(1) Self-care (self-help quitting attempt with the aid of self-help books and through mailing campaigns) [SELF HELP] (2) Five-day behavioural program [PROGRAM] (3) Nicotine patch (5 weeks) + no or minimal counselling [PATCH] (4) Nicotine patch (5 weeks) + five-day behavioural program [PATCH+PROGRAM] (5) Nicotine patch (5 weeks) + weekly individual counselling in a medical clinic (5 weekly clinic visits) [PATCH+CLINIC] (6) Nicotine patch (5 weeks) + pharmacists' consultations (five consultations) [PATCH+RPH] (7) Nicotine patch (5 weeks) + pharmacists' consultations (five consultations) + five-day behavioural program
<b>Comparators</b>	None specified
<b>Outcomes measured</b>	Net benefit of treatment [Monetary benefit (saving) to employer to produce a non-smoking employee - Cost of intervention]
<b>Healthcare and other resources considered</b>	Intervention costs [Telephone interviews to non-profit and for-profit smoking cessation program providers], cost of patch [national prescription cost data] Cost to the employer for an employee who smokes (absenteeism, medical care, discontinued lost earnings, worker's compensation, fire and accident insurance, property damage or depreciation, lost productivity, maintenance, effects of smoke)

<b>Included economic studies</b>	
	on non-smoking workers) [Review of 3 studies]
<b>Quit rate [source]</b>	[Abstinence of 6 month or longer (whether this represents point or continuous abstinence is not clear)] SELF HELP = 15% [a meta-analysis of 24 studies] PROGRAM = 28% [combining quit rates of five-day behavioural program (based on a meta-analysis of 25 studies) and group withdrawal clinic (based on a meta-analysis of 46 studies)]** PATCH = 15% [a meta-analysis of 3 studies] PATCH+PROGRAM = 26% [a meta-analysis of 4 studies] PATCH+CLINIC = 20% [a meta-analysis of 7 studies] PATCH+RPH = 31% [a national study of nicotine patch users receiving a pharmacists' consultation on smoking cessation] PATCH+RPH+PROGRAM = 44% [same source as in PATCH+RPH treatment] **Methods for combining two rates are not clearly stated
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	[Net benefit to the employer for the first year that an employee does not smoke (Based on annual cost to an employer of US\$1,483/employee who smokes)] (1) SELF HELP = US\$196, (2) PROGRAM = US\$267, (3) PATCH = US\$94, (4) PATCH+PROGRAM = US\$183, (5) PATCH+CLINIC = US\$94, (6) PATCH+RPH = US\$257, (7) PATCH+RPH+PROGRAM = US\$302
<b>Conclusion</b>	(1) Intervention strategy of PATCH (at a cost up to US\$128) +PHARM (at a cost up to US\$75)+BEH (at a cost up to US\$148) is the most cost beneficial to employers among alternatives considered (2) Adding behavioural intervention to PATCH generates greater net benefit compared with the PATCH only option
<b>Nielsen and Fiore,<sup>221</sup> 2000</b>	
<b>Country, sponsorship, study design</b>	USA Glaxo Wellcome Inc. CBA
<b>Time horizon, study perspective, population</b>	1 year Employer US employers and employees
<b>Interventions</b>	(1) Nicotine patch (8 weeks; 21mg/day for weeks 2-7, 14mg/day for week 8, 7mg/day for week 9) [PATCH] (2) Bupropion (9 weeks; 150mg/day for first 3 days, 150mg twice daily thereafter) [BUP] (3) PATCH+BUP (4) Placebo [PL] *All the interventions were administered along with self-help with minimal counselling
<b>Comparators</b>	None specified
<b>Outcomes</b>	Net benefit of treatment [Monetary benefit (saving) to employer to produce a non-

<b>Included economic studies</b>	
<b>measured</b>	smoking employee - Cost of intervention]
<b>Healthcare and other resources considered</b>	Drug costs [Average whole price; Drugs Topics Redbook], cost to health care provided visit [assumed and considered only in sensitivity analyses] Cost to the employer for an employee who smokes (= monetary benefit to employer for successful intervention) [Previous cost-benefit study], cost of work time lost for health care provider visit [assumed and considered only in sensitivity analyses]
<b>Quit rate [source]</b>	[Point prevalence rate of abstinence (since last clinic visit) at week 52; biochemically verified; quit rates are based on one RCT] PATCH = 16.4%, BUP = 30.3%, PATCH+BUP = 35.5%, PL = 15.6%
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	[Net benefit to the employer for the first year that an employee does not smoke (Based on annual cost to an employer of US\$1,654/employee who smokes)] (1) PATCH = US\$26 (2) BUP = US\$338 (3) PATCH+BUP = US\$178 (4) PL = US\$258
<b>Conclusion</b>	BUP (9 weeks, with self-help with minimal counselling) is a more cost-beneficial intervention than PATCH or PL
<b>Parrott et al,<sup>213</sup> 1998</b>	
<b>Country, sponsorship, study design</b>	UK Health Education Authority CEA
<b>Time horizon, study perspective, population</b>	40 years UK health authority, societal Smokers (general population) who seek smoking cessation interventions in England and Wales
<b>Interventions</b>	(1) Brief advice (3 minutes by GP) applied to 75% of all smokers who attempt to quit in a health authority [ADVICE] (2) Brief advice + self-help materials (1 minute by GP) [ADVICE+SELF] (3) Brief advice + self-help materials + NRT (patch) [ADVICE+SELF+NRT], (4) Brief advice + self-help materials + NRT (patch) + specialist smoking cessation service [ADVICE+SELF+NRT+SPECIAL] *Community-based interventions (e.g. No Smoking Day, Quit and Win competition) were also compared but excluded from the summary because they were not relevant interventions in our report
<b>Comparators</b>	Current practice [Brief advice (3 minutes by GP) applied to 25% of all smokers who attempt to quit in a health authority] [CP]
<b>Outcomes measured</b>	Cost per LY gained
<b>Healthcare and other resources considered</b>	NRT cost [Monthly Index of Medical Specialties], GP time [various national surveys, governmental document, previous studies], self-help material cost [assumed], cost of specialist smoking cessation clinic [previous studies with assumptions], training costs of health professionals [assumed] Patient time: traveling [Automobile association, with additional assumptions], time spent in the GP's office [National statistics with additional assumptions]
<b>Quit rate [source]</b>	[Continued abstinence at 12 month (it is not clear whether the abstinence was based on biochemical verification or self report)]

<b>Included economic studies</b>	
	ADVICE = 0.6% ADVICE+SELF = 0.8% ADVICE+SELF+NRT = 0.9% ADVICE+SELF+NRT+SPECIAL = 1.1%, CP = 1% [a previous survey] *Quit rates are based on previous studies with further adjustment by the authors (Parrott et al.) (except for CP)
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	[Cohort of 61,118 male and 58,252 female smokers who attempt to quit in an average health authority in UK (population of approximately 500,000)] <u>Health authority [or societal] perspective</u> (1) ADVICE vs. CP (i.e. ADVICE - CP) : £174 [ or £212] /life-year gained (708 life-year gained; £122,899 [or £122,899] additional cost) (2) ADVICE+SELF vs. CP: £221 [or £259] /life-year gained (945 life-year gained; £208,548 [or 244,837] additional cost) (3) ADVICE+SELF+NRT: £269 [or £696] /life-year gained (1,063 life-year gained; £286,437 [or £740,285] additional cost) (4) ADVICE+SELF+NRT+SPECIAL: £255 [or £873] /life-year gained (1,300 life-year gained; £331,156 [or £1,134,913] additional cost)
<b>Conclusion</b>	Incremental cost-effectiveness of various interventions considered ranged from £212 to £873 per discounted life year gain, which compare favourably with other health care interventions
<b>Plans-Rubio,<sup>209</sup> 1998</b>	
<b>Country, sponsorship, study design</b>	Spain Not stated CEA
<b>Time horizon, study perspective, population</b>	Lifetime Societal Smokers in Spain [age 35 to 69 (5-year age groups)]
<b>Interventions</b>	(1) Nicotine gum (2mg/day for 3 months) + Medical advice (1medical visit + 2 additional visits for those who became abstinent) [PATCH+ADVICE] (2) Nicotine patch (4mg/day for 3 months) + ADVICE [GUM+ADVICE]
<b>Comparators</b>	ADVICE only *This study focused on cost-effectiveness of interventions for the primary prevention of coronary heart disease. Therefore, interventions other than smoking cessation (e.g. cholesterol-lowering drugs, anti-hypertensive drugs) were also assessed using average cost-effectiveness ratios (not incremental ratios). However, results of these interventions were not summarized because they were not relevant to the current study.
<b>Outcomes measured</b>	Cost per LY gained (as a consequence of reduction in coronary heart disease events and mortality from lung cancer)
<b>Healthcare and other resources considered</b>	Drug costs (annual selling price) [Spanish Physician's Desk Reference], medical advice [Ministry of Health and Consumption] Savings from the prevention of CHD events (treatment cost of CHD saved, e.g. hospitalization, medical visits) [expert opinion, Ministry of Health and Consumption, Department of Health]
<b>Quit rate</b>	[1-year cessation rate (It is not clear whether or not the definition is point or

<b>Included economic studies</b>	
<b>[source]</b>	continued abstinence rate)] ADVICE = 3.8%, ADVICE+GUM = 6.7%, ADVICE+PATCH = 8.1% [previous economic studies]
<b>Relapse rate [source]</b>	Not considered
<b>Results</b>	[Cohort of 1000 smokers by age and sex] (1) PATCH+ADVICE vs. ADVICE Men: ranging from \$US4,670/life-year gained to \$US7,790/life-year gained Women: ranging from \$US7,910/life-year gained to \$US11,420/life-year gained (2) GUM+ADVICE vs. ADVICE Men: ranging from \$US3,950/life-year gained to \$US6,580/life-year gained Women: ranging from \$US6,680/life-year gained to \$US9,660/life-year gained
<b>Conclusion</b>	In reference to ADVICE, GUM+ADVICE is more cost-effective than PATCH+ADVICE
<b>Shanahan et al,<sup>203</sup> 2003</b>	
<b>Country, sponsorship, study design</b>	Australia Not stated CEA
<b>Time horizon, study perspective, population</b>	12 months Payers (government or patients) Australian general population of smokers
<b>Interventions</b>	(1) Bupropion (9 weeks) + GP visit (1 visit) [BUP+GP] (2) Prescription NRT patch (12 to 16 weeks) + GP visit (3 visits) [PATCH+GP] (3) Over-the-counter NRT patch [OTC_PATCH]
<b>Comparators</b>	None specified
<b>Outcomes measured</b>	Cost per additional quitter
<b>Healthcare and other resources considered</b>	Drug costs & GP visit [Department of Health and Ageing, Health Insurance Commission]
<b>Quit rate [source]</b>	[12-month quit rate (it is not clear whether this is point or continued abstinence rate)] (1) BUP+GP = 21% to 35%, (2) PATCH+GP or OTC_PATCH = 14% to 21% [previous trials, no meta-analysis]
<b>Relapse rate [source]</b>	N/A
<b>Results</b>	<u>Effectiveness</u> BUP+GP is more effective than PATCH+GP or OTC_PATCH <u>Total cost to the government</u> (1) BUP+GP = A\$263.34 (2) PATCH+GP = A\$444.43 (3) OTC_PATCH = no cost <u>Total cost to patients</u> (1) BUP+GP = A\$28.76 (2) PATCH+GP = A\$35.48 (3) OTC_PATCH = A\$396.00

<b>Included economic studies</b>	
<b>Conclusion</b>	BUP is more effective and less expensive compared with PATCH both for government and for the patient
<b>Shearer and Shanahan,<sup>201</sup> 2006</b>	
<b>Country, sponsorship, study design</b>	Australia Australian Government Department of Health and Ageing CEA
<b>Time horizon, study perspective, population</b>	6 month Australian government General population of smokers in Australia
<b>Interventions</b>	(1) Brief advice (by a health professional; booklet + 2 GP visits) [ADVICE] (2) Telephone counselling (booklet + 20-70 minute counselling) [COUNSEL] (3) Nicotine patches (10 weeks) + COUNSEL [PATCH+COUNSEL] (4) PATCH+ Proactive telephone counselling (booklet + 47 minute counselling (with active telephone calls)) [PATCH+PROCOUNSEL] (5) Bupropion (9 weeks) + COUNSEL [BUP+COUNSEL] (6) BUP+PROCOUNSEL (7) BUP+PATCH+COUNSEL
<b>Comparators</b>	None considered
<b>Outcomes measured</b>	Cost per additional quitter
<b>Healthcare and other resources considered</b>	Intervention cost (drugs, booklets, counselling) [Australian Federal Government, Pharmaceutical Benefits Schedule, Medical Benefits Schedule]
<b>Quit rate [source]</b>	[Abstinence at 6 months or longer, either continuous or point prevalence] (1) ADVICE = 6% [2 meta-analyses (7 and 16 trials each)] (2) COUNSEL = 9% [1 meta-analysis (27 trials)] (3) PATCH+COUNSEL = 17% [a meta-analysis (96 trials)] (4) PATCH+PROCOUNSEL = 27% [1 RCT] (5) BUP+COUNSEL = 19% [1 meta-analysis (16 trials)] (6) BUP+PROCOUNSEL = 32% [1 trial] (7) BUP+PATCH+COUNSEL = 19% [2 separate trials] *In their cost-effective analyses, a natural quit rate of 4% were subtracted from the efficacy of each treatment strategy
<b>Relapse rate [source]</b>	N/A
<b>Results</b>	(for a treatment of 100 patients) <u>Comparisons associated with nicotine replacement therapy</u> (1) PATCH+COUNSEL vs. COUNSEL (i.e. PATCH+COUNSEL - COUNSEL): A\$4,767/additional quitter (additional costs = A\$38,134, additional % quitting = 8%) (2) PATCH+PROCOUNSEL vs. PATCH+COUNSEL: A\$151/additional quitter (additional costs = A\$1,505, additional % quitting = 10%) (3) BUP+PATCH+COUNSEL vs. PATCH+COUNSEL: A\$14,340/additional quitter (additional costs = A\$28,679, additional % quitting = 2%) <u>Comparisons associated with bupropion</u> (1) BUP+COUNSEL vs. COUNSEL: A\$3,225 (additional costs = A\$32,249, additional % quitting = 10%)

<b>Included economic studies</b>	
	<p>(2) BUP+PROCOUNSEL vs. BUP+COUNSEL: A\$116 (additional costs = A\$1,505, additional % quitting = 13%)</p> <p>(3) BUP+PATCH+COUNSEL vs. BUP+PROCOUNSEL: BUP+PROCOUNSEL is more effective and less expensive</p> <p><u>Comparison among behavioural interventions</u></p> <p>(1) COUNSEL vs. ADVICE: COUNSEL more effective and less expensive (additional costs = -\$A791, additional % quitting = 3%)</p>
<b>Conclusion</b>	<p>(1) Telephone counselling appeared to be the most cost-effective method among alternative interventions considered. Therefore, GPs are encouraged to provide telephone counselling and, if prescribing pharmacotherapy, use a combination therapy of pharmacotherapy and telephone counselling</p> <p>(2) Bupropion appear to be more cost-effective than those with NRT patches</p> <p>(3) Adding PROCOUNSEL to pharmacotherapy appear to be cost-effective (improved outcomes at small additional cost)</p>
<b>Woolacott et al,<sup>212</sup> 2002</b>	
<b>Country, sponsorship, study design</b>	<p>UK</p> <p>None declared</p> <p>CEA, CUA</p>
<b>Time horizon, study perspective, population</b>	<p>Lifetime</p> <p>UK National Health Services</p> <p>Adult smokers who attempt to quit smoking in England and Wales</p>
<b>Interventions</b>	<p>(1) Nicotine Replacement Therapy (NRT) + Brief advice (or counselling) (including doctor's advice or more intensive counselling by other health professionals) [NRT+ADVICE (or COUNSEL)]</p> <p>(2) Bupropion + ADVICE [BUP+ADVICE (or COUNSEL)]</p> <p>(3) NRT+BUP+ADVICE (or COUNSEL)</p>
<b>Comparators</b>	ADVICE (or COUNSEL) only
<b>Outcomes measured</b>	Cost per quitter, Cost per life-year saved, Cost per QALY gained
<b>Healthcare and other resources considered</b>	Treatment costs (drugs, counselling, brief advice from GP) [previous studies, National Health Services]
<b>Quit rate [source]</b>	<p>[Continuous abstinence at 12 month, based on either biochemically verified or self report]</p> <p>(1) Spontaneous cessation = 1% [a previous economic study]</p> <p>(2) Advice only = 3% (excluding spontaneous cessation) [a previous economic study]</p> <p>(3) Counselling only = 9% (excluding spontaneous cessation) [a previous economic study]</p> <p>(4) NRT (NRT vs. placebo) = odds ratio = 1.67 [a meta-analysis of 70 RCTs]</p> <p>(5) BUP (BUP vs. placebo) = odds ratio = 2.1 [a meta-analysis of 4 trials and unpublished studies],</p> <p>(6) BUP+NRT (BUP+NRT vs. placebo) = odds ratio = 2.65 [1 trial]</p>
<b>Relapse rate [source]</b>	Life-time relapse rate = 40% [assumed]
<b>Results</b>	<p>Cost per additional life-time (LT) quitter</p> <p>(1) ADVICE+NRT vs. ADVICE: £4,798/LT quitter</p> <p>(2) ADVICE+BUP vs. ADVICE: £2,986/LT quitter</p>

<b>Included economic studies</b>	
	<p>(3) ADVICE+NRT+BUP vs. ADVICE: £3,939/LT quitter  (4) ADVICE+NRT vs. ADVICE+BUP: £62/LT quitter  (5) ADVICE+NRT+BUP vs. ADVICE+NRT : £3,314/LT quitter  (6) ADVICE+NRT+BUP vs. ADVICE+BUP: £5,981/LT quitter  (7) COUNSEL+NRT vs. COUNSEL: £2,001/LT quitter  (8) COUNSEL+BUP vs. COUNSEL: £1,278/LT quitter  (9) COUNSEL+NRT+BUP vs. COUNSEL: £1,781/LT quitter  (10) COUNSEL+NRT vs. COUNSEL+BUP: £30/LT quitter  (11) COUNSEL+NRT+BUP vs. COUNSEL+NRT: £1,606/LT quitter  (12) COUNSEL+NRT+BUP vs. COUNSEL+BUP: £2,952/LT quitter</p> <p><u>Cost per life-year (LY) gained (assume 2 LY saved per quitter)</u>  (1) ADVICE+NRT vs. ADVICE: £2,399/LY gain  (2) ADVICE+BUP vs. ADVICE: £1,493/LY gain  (3) ADVICE+NRT+BUP vs. ADVICE: £1,969/LY gain  (4) COUNSEL+NRT vs. COUNSEL: £1,000/LY gain  (5) COUNSEL+BUP vs. COUNSEL: £639/LY gain  (6) COUNSEL+NRT+BUP vs. COUNSEL: £890/LY gain</p> <p><u>Cost per QALY gained (assume 2.7 QALY per quitter)</u>  (1) ADVICE+NRT vs. ADVICE: £1,777/QALY gain  (2) ADVICE+BUP vs. ADVICE: £1,106/QALY gain  (3) ADVICE+NRT+BUP vs. ADVICE: £1,459/QALY gain  (4) COUNSEL+NRT vs. COUNSEL: £741/QALY gain  (5) COUNSEL+BUP vs. COUNSEL: £473/QALY gain  (6) COUNSEL+NRT+BUP vs. COUNSEL: £660/QALY gain</p>
<b>Conclusion</b>	<p>(1) Pharmacological interventions for smoking cessation are cost-effective compared with other interventions  (2) Incremental cost-effectiveness of BUP is generally better than that of NRT. However, evidence on relative efficacy of BUP and potential side effects is lacking</p>

## APPENDIX 13: QUALITY ASSESSMENT OF ECONOMIC STUDIES

Quality assessment of included economic studies <sup>4</sup>										
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Akehurst and Piercy <sup>214</sup>	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Bertman et al <sup>202</sup>	Y	Y	Y	Y	Y	Y	NC	Y	Y	Y
Bolin et al <sup>210</sup>	Y	NC	Y	Y	Y	Y	Y	Y	Y	Y
Bolin et al <sup>211</sup>	Y	NC	Y	Y	Y	NC	Y	Y	Y	N
Cornuz et al <sup>225</sup>	Y	Y	Y	Y	Y	NC	Y	Y	Y	N
Feenstra et al <sup>205</sup>	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Flack et al <sup>215</sup>	Y	Y	NC	Y	Y	Y	Y	Y	Y	NC
Gilbert et al <sup>208</sup>	Y	Y	NC	Y	Y	Y	Y	Y	Y	Y
Hall et al <sup>216</sup>	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y
Halpern et al <sup>217</sup>	Y	Y	Y	Y	Y	Y	NC	Y	N	Y
Halpern et al <sup>223</sup>	Y	Y	NC	Y	Y	Y	Y	Y	N	N
Heitjan et al <sup>222</sup>	Y	Y	Y	N	Y	Y	Y	Y	Y	N
Hill <sup>218</sup>	Y	NC	Y	Y	Y	Y	NA	Y	Y	Y
Hoogendoorn et al <sup>206</sup>	Y	Y	Y	Y	NC	NC	Y	Y	Y	Y
Howard et al <sup>219</sup>	Y	Y	Y	Y	Y	N	Y	Y	Y	N
Igarashi et al <sup>204</sup>	Y	Y	Y	Y	NC	Y	Y	Y	Y	N
Jackson et al <sup>220</sup>	Y	Y	Y	Y	Y	NC	NA	Y	NC	N
Kaper et al <sup>207</sup>	Y	Y	Y	Y	Y	NC	Y	Y	Y	N
McGhan and Smith <sup>224</sup>	Y	Y	N	Y	Y	Y	NA	Y	Y	Y
Nielsen and Fiore <sup>221</sup>	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y
Parrott et al <sup>213</sup>	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Plans-Rubio <sup>209</sup>	Y	Y	NC	NC	Y	Y	Y	Y	NC	Y
Shanahan <sup>203</sup>	Y	Y	NC	Y	Y	Y	NA	Y	N	Y
Shearer and Shanahan <sup>201</sup>	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y
Woolacott et al <sup>212</sup>	Y	Y	Y	N	Y	Y	NA	Y	Y	N

Y: yes, N: no, NC: not clear; NA: not applicable

### Description of questions:<sup>4</sup>

**Q1:** Was a well-defined question posed in answerable form?

**Q2:** Was a comprehensive description of the competing alternatives given?

**Q3:** Was the effectiveness of the programmes or services established?

**Q4:** Were all the important and relevant costs and consequences for each alternative identified?

**Q5:** Were costs and consequences measured accurately in appropriate physical units?

**Q6:** Were costs and consequences valued credibly?

**Q7:** Were costs and consequences adjusted for differential timing?

**Q8:** Was an incremental analysis of costs and consequences of alternatives performed?

**Q9:** Was allowance made for uncertainty in the estimates of costs and consequences?

**Q10:** Did the presentation and discussion of study results include all issues of concern to users?

# APPENDIX 14: TRANSITION PROBABILITIES FOR CHRONIC CONDITION MODEL

A total of 68 transition probabilities were used to describe transitions of developing smoking-related chronic conditions and transitions among various smoking-related chronic conditions (Figure 9). For most cases, transition probabilities were identified by a review of existing economic evaluation studies found through the Tufts Cost-Effectiveness Registry database.<sup>243</sup>

## Section I. Transition probabilities from “No morbidity” state to chronic disease states

Incidence data were used to describe transitions from “No morbidity” state to chronic condition states. Transition probabilities from “No morbidity” to chronic condition states were based on the incidence data obtained from a review of literature and other published sources. However, they were not stratified by smoking status. Therefore, we calibrated the incidence data using (a) relative risk of developing each chronic condition by smoking status and (b) prevalence of smoking status to obtain incidence rates by smoking status as follows:<sup>204</sup>

First, incidence rates for non-smokers were calculated. For each chronic condition state, we defined age- and sex- specific total incidence rates as  $I_{Tij}$ , where these rates were obtained based on a review of published literature (shown in Table A11) ( $i$  = age;  $j$  = male or female). We also defined age- and sex-specific incidence rates for non-smokers, smokers and quitters as  $I_{NSij}$ ,  $I_{Sij}$  and  $I_{Qij}$  respectively.

Age- and sex-specific relative risk of a disease for smokers versus non-smokers was defined as  $RR_{Sij}$ , and age- and sex-specific relative risk of a disease for former smokers (quitters) versus non-smokers was defined as  $RR_{Qij}$ . These age- and sex-specific relative risks are shown in Table A12.

Also consider the age- and sex-specific prevalence of non-smokers, smokers and quitters over the total population as  $NS_{ij}$ ,  $S_{ij}$  and  $Q_{ij}$  respectively. These prevalence data are shown in Table A15.

Using these data, the following equations hold:

$$(1) I_{Tij} = I_{NSij} * (NS_{ij}) + I_{Sij} * (S_{ij}) + I_{Qij} * (Q_{ij}), \text{ and}$$

$$(2) I_{Sij} = RR_{Sij} * I_{NSij}$$

$$(3) I_{Qij} = RR_{Qij} * I_{NSij}$$

From (1) to (3),

$$I_{Tij} = I_{NSij} * (NS_{ij}) + RR_{Sij} * I_{NSij} * (S_{ij}) + RR_{Qij} * I_{NSij} * (Q_{ij})$$

Rearranging the above gives:

$$I_{Tij} = I_{NSij} * [NS_{ij} + RR_{Sij} * (S_{ij}) + RR_{Qij} * (Q_{ij})]$$

i.e.,

$$I_{NSij} = I_{Tij} / [NS_{ij} + RR_{Sij} * (S_{ij}) + RR_{Qij} * (Q_{ij})]$$

Once  $I_{NSij}$  is obtained, equations (2) and (3) were used to get  $I_{Sij}$  and  $I_{Qij}$ .

For CHD and stroke states, original data were presented as probabilities.<sup>474,475</sup> Therefore, to use the above formula, annual probabilities ( $p$ ) were converted to rates ( $r$ ) using the following formula:  $r = -[\ln(1-p)]$ .<sup>236</sup>

Once incidence rates by age, sex, and smoking status for each chronic condition were obtained, they were transformed to annual transition probabilities using the following formula:

$$p = 1 - \exp(-r * t)$$

where  $r$  is the rate (per person-year or population) and  $t$  is the time period of interest (here  $t=1$ ).<sup>236</sup>

Unless data were available (such as lung cancer and initial MI), we assumed that the probabilities of developing these chronic conditions were zero for those under the age of 30 years, due to the very low prevalence of these conditions under the age of 30 years. For asthma exacerbation state, non-zero transition probabilities were assumed for those under the age of 30 years. We did not consider these transition probabilities as probabilistic because incidence data obtained were based on population-level registry data.<sup>205,476-478</sup> For other sources, we did not have sufficient information to make these transition probabilities probabilistic.<sup>210,247,474,479,480</sup>

## **Section II. Transition probabilities across chronic disease states**

Other transition probabilities represent conditional probabilities of developing a new smoking-related condition (or mortality) for those who already have a certain smoking-related condition. We assumed that, once a cohort developed a smoking-related chronic condition, further transitions to other chronic states only depended on the existing condition, age and/or sex and did not depend on smoking status. In addition, it was assumed that, in each chronic condition state, a cohort faced a probability of developing an asthma exacerbation as co-morbidity. We assumed that the probability of developing asthma exacerbation was independent of the co-morbidity status [i.e.,  $p(\text{asthma exacerbation} | \text{any existing chronic condition}) = p(\text{asthma exacerbation} | \text{no morbidity})$ ].

For each health state, transition probabilities are summarized below. Age-specific transition probabilities associated with a number of cardiovascular states were based on Karnon et al.<sup>244</sup>

<b>Table A1: Transition probabilities from PVD-AAA state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>PVD-AAA to:</b>			
PVD-AAA	Complement	n/a	n/a
Initial stroke	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
Initial TIA*	Male: 0.00689 Female: 0.00813	Fixed***	Caro et al <sup>481</sup>
Initial MI	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
COPD**	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer**	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>

\*Based on Saskatchewan population health care administrative database (n = 16,400 patients over 21 years old who had initial diagnosis of PVD in Saskatchewan between 1985 and 1995).

\*\* Literature searches did not find appropriate sources describing the probability of PVD-AAA patients developing COPD or lung cancer.

\*\*\*Transition probabilities were based on population-level administrative database, therefore, assumed to be fixed.  
n/a: not applicable

<b>Table A2: Transition probabilities from Stroke state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>Stroke to:</b>			
Stroke	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
Post stroke	Complement	n/a	n/a
COPD*	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer*	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>

\* Literature searches did not find appropriate sources describing the probability of stroke patients developing COPD or lung cancer.

n/a: not applicable

<b>Table A3: Transition probabilities from Post Stroke state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>Post stroke to:</b>			
Post stroke	Complement	n/a	n/a
Stroke	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
COPD*	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer*	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>

\* Literature searches did not find appropriate sources describing the probability of post stroke patients developing COPD or lung cancer.

n/a: not applicable

Table A4: Transition probabilities from TIA state			
Health States	Annual probability	Distribution	Source
<b>TIA to:</b>			
TIA*	0.123	Fixed	Hill et al. <sup>482</sup>
Post TIA	Complement	n/a	n/a
PVD-AAA**	Assumed to be the same as the incidence of PVD-AAA	n/a	n/a
Initial stroke***	Male: 0.02197 Female: 0.02311 (zero for those aged < 40)	Male: Beta [alpha = 83, beta = 492 (=575-83)] Female: Beta [alpha = 36, beta = 203 (=239-36)]	Farrell et al. <sup>483</sup>
CHD**	Assumed to be the same as the incidence of CHD	n/a	n/a
Initial MI <sup>§</sup>	0.01062	Beta [alpha = 23, beta = 419 (=442-23)]	The American-Canadian Co-Operative Study Group <sup>484</sup>
COPD <sup>†</sup>	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer <sup>†</sup>	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead <sup>‡</sup>	Assumed to be the same as all-cause mortality	n/a	n/a

[The data selection above were based on a review of 13 articles retrieved to identify transition probabilities associated with TIA]

\*Hill et al. provided the incidence of recurrent TIA at one year based on four administrative databases (hospital inpatient, emergency department visit, vital statistics, and claims database) representative of residents in the Province of Alberta. We also found an alternative source targeting US and Canadian samples (the American-Canadian Co-Operative Study Group<sup>484</sup>), which was included in a systematic review and meta-analysis by Touze et al.<sup>485</sup> However, The American-Canadian Co-Operative Study Group<sup>484</sup> was an RCT study, hence the sample may not be as representative as that reported in Hill et al. Because the transition probability was based on an administrative database, it was assumed to be fixed.

\*\*Literature searches did not find appropriate sources describing the probability of TIA patients developing PVD-AAA and CHD.

\*\*\*This article was included in a recent systematic review and a meta-analysis of 38 studies targeting TIA and ischemic stroke patients (Touze et al.<sup>485</sup>). Of the 38 studies included, two studies<sup>483,484</sup> targeted TIA patients only. However, only Farrell et al. reported stroke as an outcome. Therefore, we used the probability of minor, major, or fatal stroke for TIA patients in the placebo group reported in Farrell et al. The target population in Farrell et al. was those over 40 years old. Therefore, transition probabilities for those under the age of 40 were assumed to be zero. This was a reasonable assumption considering that the prevalence of stroke is considered to be small for those under the age of 40 years (e.g., the proportion of those under the age of 40 years who responded to have effects of stroke was approximately 3% of the total respondents who reported to have suffered from effects of stroke<sup>252</sup>). Annual transition probabilities were calculated based on the proportion of males (n=575) and females (n=239) who developed stroke (minor, major or fatal) during the seven-year study period, which were 14.4% and 15.1% respectively. Then the seven-year probabilities were converted to the annual probabilities. Probabilistic analyses were conducted around the seven-year event probabilities.

<sup>§</sup> Two studies<sup>483,484</sup> were found as a potential source. However, outcomes reported in Farrell et al.<sup>483</sup> was the composite outcome of coronary event (non-fatal MI or fatal ischemic heart disease) for TIA patients. Therefore, The American-Canadian Co-Operative Study Group,<sup>484</sup> which provided the probability of MI for TIA patients [in a placebo group of their trial (n=442)], was selected. Of 442 study subjects with TIA, 23 (5.2%) suffered MI over the five-year study period. Based on the five-year event probability, annual probability was calculated. Probabilistic analyses were conducted around the five-year event probability.

<sup>†</sup> Literature searches did not find appropriate sources describing the probability of TIA patients developing COPD or lung cancer.

<sup>‡</sup> Death caused by TIA can be considered as negligible. Therefore we assumed that there was no excess mortality due to TIA.

n/a: not applicable

<b>Table A5: Transition probabilities from Post TIA state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>Post TIA to:</b>			
Post TIA	Complement	n/a	n/a
TIA	Assumed to be the same as the probability from TIA to TIA	n/a	n/a
PVD-AAA	Assumed to be the same as the probability from TIA to PVD-AAA	n/a	n/a
Initial stroke	Assumed to be the same as the probability from TIA to Initial stroke	n/a	n/a
CHD	Assumed to be the same as the probability from TIA to CHD	n/a	n/a
Initial MI	Assumed to be the same as probability from TIA to Initial MI	n/a	n/a
COPD*	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer*	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead	Assumed to be the same as the probability of TIA to death	n/a	n/a

\* Literature searches did not find appropriate sources describing the probability of post TIA patients developing COPD or lung cancer.

n/a: not applicable

<b>Table A6: Transition probabilities from MI state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>MI to:</b>			
MI	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
Stroke	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
Post MI	Complement	n/a	n/a
COPD*	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer*	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>

\*Literature searches did not find appropriate sources describing the probability of MI patients developing COPD or lung cancer.

n/a: not applicable

<b>Table A7: Transition probabilities from Post MI state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>Post MI to:</b>			
Post MI	Complement	n/a	n/a
MI	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
Stroke	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>
COPD*	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer*	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead	Age specific	Normal (around estimated coefficients on logistic regressions)	Karnon et al <sup>244</sup>

\*Literature searches did not find appropriate sources describing the probability of post MI patients developing COPD or lung cancer.

n/a: not applicable

<b>Table A8: Transition probabilities from CHD state<sup>§</sup></b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>CHD to:</b>			
CHD	Complement	n/a	n/a
Stroke*	0.00705	Beta [alpha = 17, beta = 783 (= 800-17)]	Athyros et al <sup>486</sup>
MI*	0.02181	Beta [alpha = 51, beta = 749 (= 800-51)]	Athyros et al <sup>486</sup>
COPD**	Assumed to be the same as the incidence of COPD	n/a	n/a
Lung cancer**	Assumed to be the same as the incidence of lung cancer	n/a	n/a
Dead***	0.0516	Beta [alpha = 128, beta = 542 (= 670-128 )]	Raftery et al <sup>487</sup>

<sup>§</sup>Based on a review of 9 papers retrieved to identify transition probabilities associated with CHD

\*Athyros et al.<sup>486</sup> was an RCT study targeting patients with established CHD (n=1,600) in Greece. We used outcomes of patients randomized to receive “usual care” (n=800). The transition probability from CHD to Stroke referred to the outcome of stroke event; the transition probability from CHD to MI referred to the outcome of non-fatal MI. During the three-year follow-up, 17 (2.1%) developed stroke and 51 (6.4%) developed non-fatal MI. Probabilistic analyses were conducted around the three-year event probabilities. Because the study was based on patients under the age of 75 years, we assumed that the transition probabilities for those aged over 75 years were same as those for patients under the age of 75 years. Another source considered was a report by National Collaborating Centre for Chronic Conditions.<sup>488</sup> The transition probabilities reported, however, were stroke or MI incidence conditional on the existence of unstable angina.

\*\*Literature searches did not find appropriate sources describing the probability of CHD patients developing COPD or lung cancer.

\*\*\*Raftery et al. was based on a four-year follow-up of an RCT conducted in north-east Scotland (in 19 general practices). Total mortality rate from CHD patients in a control group (usual care; n=670) was used. During the four-year study period, 128 (19.1%) died. The target population of the study was those under 80 years old. Therefore, it was assumed that the death rate was same for those over the age of 80 years. Probabilistic analyses were conducted around the four-year event probability.

n/a: not applicable

<b>Table A9: Transition probabilities from COPD state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>COPD to:</b>			
COPD	Complement	n/a	n/a
Lung cancer*	Assumed to be 2.1 times of the incidence of lung cancer compared with those with normal lung function based on the relative risk of lung cancer for those with normal lung function versus those with COPD	Normal [around log of relative risk (ln(RR)); mean (ln(RR)) = 0.7419 and SE (ln(RR)) = 0.3347]	Purdue et al <sup>489</sup>
Dead**	0.07948	Beta [alpha = 80, beta = 290 (= 370-80)]	Briggs et al <sup>490</sup>

\*Based on a review of 31 studies. In Purdue et al.,<sup>489</sup> relative risk of lung cancer by lung function type (normal, mild COPD, moderate COPD, severe COPD and restrictive lung disease) were presented based on a cohort of Swedish construction workers (n=176,997) who underwent spirometric evaluation between 1971 and 1993, and the 2001 Swedish National Cancer Registry. Using relative risk of 2.1 (95% CI = 1.7-2.6) for those with moderate COPD (versus those with normal lung function), we adjusted the age, sex and smoking status-specific transition probability from no morbidity to COPD (i.e., incidence of COPD) by multiplying those probabilities by 2.1. Probabilistic analyses were conducted around the natural log of the relative risk estimate (= 0.7419) with the standard error of the natural log of relative risk of 0.3347 (= [ln(2.6)-ln(1.7)]/[2\*1.96]).

\*\*Based on a review of 16 studies. Briggs et al.<sup>490</sup> was based on a trial (n=751) targeting patients with moderate to severe COPD in UK. We considered a total mortality rate for those in the placebo group (n=370) as the transition probability from COPD to death. During the three-year period, approximately 80 (22%) patients in the placebo group died. Probabilistic analyses were conducted around the three-year death probability.

n/a: not applicable

<b>Table A10: Transition probabilities from Lung cancer state</b>			
<b>Health States</b>	<b>Annual probability</b>	<b>Distribution</b>	<b>Source</b>
<b>Lung cancer to:</b>			
Lung cancer	Complement	n/a	n/a
Dead*	<u>Male</u> Age 30-39 = 0.494 Age 40-49 = 0.546 Age 50-59 = 0.550 Age 60-69 = 0.563 Age 70-79 = 0.613 Age 80+ = 0.710 <u>Female</u> Age 30-39 = 0.386 Age 40-49 = 0.449 Age 50-59 = 0.453 Age 60-69 = 0.478 Age 70-79 = 0.549 Age 80+ = 0.673	Fixed**	National Cancer Institute <sup>491</sup>

\*Based on 12-month cause-specific survival rates of lung cancer for those diagnosed between 2000 and 2006.

\*\* Probabilities were based on national surveillance data, therefore, assumed to be fixed.

n/a: not applicable

Table A11: Incidence (per person year) of chronic conditions by age and sex*								
Age	COPD	Lung cancer	CHD	Stroke	Asthma	MI	PVD-AAA	TIA
<b>Male</b>								
18-24	0	0	0	0	0.00792	0	0	0
25-29	0	0.000005	0	0	0.00792	0.0001	0	0
30-34	0	0.000007	0.0017	0.0003	0.00792	0.0002	0.0006	0.00010
35-39	0.00623	0.000028	0.0034	0.0003	0.00516	0.0005	0.0006	0.00010
40-44	0.00623	0.000083	0.0057	0.0003	0.00516	0.0013	0.0006	0.00010
45-49	0.00623	0.000217	0.0089	0.0003	0.00516	0.0028	0.0019	0.00010
50-54	0.00623	0.000538	0.0120	0.0003	0.00516	0.0046	0.0019	0.00010
55-59	0.00623	0.001091	0.0159	0.0003	0.00516	0.0061	0.0053	0.00010
60-64	0.00623	0.002100	0.0207	0.0003 <sup>a</sup> 0.0034 <sup>b</sup>	0.00516	0.0088	0.0053	0.00010
65-69	0.00623	0.003313	0.0266	0.0034 <sup>c</sup> 0.0038 <sup>d</sup>	0.01384	0.0139	0.0061	0.00010
70-74	0.01887	0.004452	0.0273	0.0038 <sup>e</sup>	0.01384	0.0120	0.0061	0.00010
75-79	0.01887	0.005406	0.0273	0.0046 <sup>f</sup> 0.0054 <sup>g</sup>	0.01384	0.0148	0.0061	0.00010
80-84	0.01887	0.005501	0.0273	0.0054 <sup>h</sup> 0.0062 <sup>i</sup>	0.01384	0.0165	0.0061	0.00010
85+	0.01887	0.004927	0.0273	0.0078	0.01384	0.0326	0.0061	0.00147
<b>Female</b>								
18-24	0	0	0	0	0.00792	0	0	0
25-29	0	0.000007	0	0	0.00792	0	0	0
30-34	0	0.000011	0.0002	0.0015	0.00792	0.0001	0.0003	0.00010
35-39	0.00505	0.000026	0.0003	0.0015	0.00516	0.0002	0.0003	0.00010
40-44	0.00505	0.000127	0.0012	0.0015	0.00516	0.0004	0.0003	0.00010
45-49	0.00505	0.000343	0.0027	0.0015	0.00516	0.0007	0.0007	0.00010
50-54	0.00505	0.000555	0.0049	0.0015	0.00516	0.0008	0.0007	0.00010
55-59	0.00505	0.000942	0.0078	0.0015	0.00516	0.0010	0.0018	0.00010
60-64	0.00505	0.001597	0.0094	0.0015 <sup>a</sup> 0.0019 <sup>b</sup>	0.00516	0.0030	0.0018	0.00010
65-69	0.00505	0.002189	0.0107	0.0019 <sup>j</sup>	0.01384	0.0048	0.0054	0.00010
70-74	0.01274	0.002848	0.0128	0.0030 <sup>k</sup> 0.0034 <sup>l</sup>	0.01384	0.0069	0.0054	0.00010
75-79	0.01274	0.003127	0.0128	0.0034 <sup>m</sup> 0.0038 <sup>n</sup>	0.01384	0.0091	0.0054	0.00010
80-84	0.01274	0.002758	0.0128	0.0038 <sup>o</sup> 0.0046 <sup>p</sup>	0.01384	0.0112	0.0054	0.00010
85+	0.01274	0.002034	0.0128	0.0046	0.01384	0.0139	0.0054	0.00147

<sup>a</sup>: age 60 to 62, <sup>b</sup>: age 63 and 64, <sup>c</sup>: age 65-68, <sup>d</sup>: age 69, <sup>e</sup>: 70-75, <sup>f</sup>: age 76-78, <sup>g</sup>: age 79, <sup>h</sup>: age 80 and 81, <sup>i</sup>: age 82-84, <sup>j</sup>: age 65-70, <sup>k</sup>: age 71-73, <sup>l</sup>: age 74, <sup>m</sup>: age 75-78, <sup>n</sup>: age 79, <sup>o</sup>: age 80 and 81, <sup>p</sup>: age 82-84

**\*Data source and selection:**

**COPD:** Incidence of COPD was obtained based on a review of 17 studies found from a literature review. We selected the incidence of COPD reported in Bolin et al.<sup>210</sup> The incidence (per 100,000 population) for the periods between 1990-1991 and 1998-1999 was derived from the Swedish Survey of Living Conditions. We also found data reported by the Canadian Institute for Health Information (CIHI) and others.<sup>492</sup> However, the data was limited to COPD hospitalization rates.

**Lung cancer:** We identified 25 potentially relevant articles to identify the incidence of lung cancer. Among these, we found that the age- and sex-specific incidence of lung cancer (per 100,000 population) in 2005 Canadian cancer surveillance data reported by Public Health Agency of Canada to be the most comprehensive and representative source.<sup>477,478</sup>

**CHD:** Of the 18 studies reviewed for the incidence of CHD, we selected predicted six-year probabilities of developing CHD by age and sex reported in Anderson et al.,<sup>474</sup> which was based on 5,573 subjects in the Framingham Heart Study data. Other studies that we found were based on data from European countries, randomized controlled trials, and/or restrictive target populations.

**Stroke:** Canadian surveillance information for cardiovascular diseases was limited.<sup>476</sup> McCormack et al. presented the 10-year risk of a cerebrovascular event (atherothrombotic brain infarction, transient ischemic attack, cerebral embolism, intracerebral hemorrhage, and subarachnoid hemorrhage) for those without history of cerebrovascular disease.<sup>475,493</sup> The data were based on the Framingham study. Because the reported risk was a composite of cerebrovascular events, of the total reported risk, the incidence of initial stroke was calculated as 75% for males and 80% for females, assuming that, of total cerebrovascular events, TIA accounted for approximately 25% for males and 20% for females.<sup>475</sup> (1 study reviewed)

**Asthma exacerbation:** We considered the number of emergency department visits as a proxy for the incidence of asthma exacerbation. Moorman et al.<sup>247</sup> provided the estimated age-specific rate (per 10,000 population) of emergency department visits for asthma based on the 2004 US National Hospital Ambulatory Medical Care Survey data. Combining this data with data on the estimated average number of emergency department visits for asthma during 2001-2003 for males and females (also provided in Moorman et al.<sup>247</sup>), we calculated the estimated age- and sex-specific rate of asthma emergency department visit. (8 studies reviewed)

**MI:** Incidence of initial MI was from age- and sex-specific incidence (per 1,000 person years) of acute MI in 1994 based on two registry systems in general practice in the Netherlands.<sup>205</sup> We also found data based on a study targeting Nova Scotia and Saskatchewan.<sup>494</sup> However, the Canadian data was not as comprehensive as that in Hoogenveen et al., and was older than that of the Dutch study. (2 studies reviewed)

**PVD-AAA:** We considered the age- and sex-specific incidence (per 10,000 population) of intermittent claudication to represent the incidence of PVD-AAA. The incidence rate was based on the 14-year follow-up of the Framingham Study.<sup>479,480</sup> Other papers reported incidence rates specific to PVD or AAA,<sup>204,248,495</sup> and/or the target population was limited.<sup>204,248</sup> (4 studies reviewed)

**TIA:** Incidence rates of initial TIA were taken from Bejot et al.,<sup>496</sup> which was age-specific standardized (to the world population) incidence rates of first-ever TIA (per 100,000 per year). This US population-based study reported age, sex, and race-specific incidence of TIA. However, the rates were the combined rates of first-ever and recurrent TIA.<sup>497</sup> Although an Alberta-based study reported the incidence of first-ever TIA, only the crude incidence rates were reported.<sup>482</sup> (8 studies reviewed)

Table A12: Relative risk* of developing chronic conditions						
Health State	RR	SE	Distribution	RR	SE	Distribution
	<b>COPD</b> <sup>219,246</sup>			<b>Lung cancer</b> <sup>219,246</sup>		
<b>Male smoker</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35+	10.8	0.128 <sup>‡</sup>	Lognormal	21.3	0.094 <sup>‡</sup>	Lognormal
<b>Female smoker</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35+	12.3	0.111 <sup>‡</sup>	Lognormal	12.5	0.070 <sup>‡</sup>	Lognormal
<b>Male quitter</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35+	7.8	0.125 <sup>‡</sup>	Lognormal	8.3	0.094 <sup>‡</sup>	Lognormal
<b>Female quitter</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35+	8.9	0.115 <sup>‡</sup>	Lognormal	4.8	0.080 <sup>‡</sup>	Lognormal
	<b>TIA</b> <sup>250***</sup>			<b>PVD-AAA</b> <sup>248**</sup>		
<b>Smoker</b>	1.13	0.252	Lognormal	2.4	0.242 <sup>†</sup>	Lognormal
<b>Quitter</b>	1.0	n/a	Fixed	2.4	0.242 <sup>†</sup>	Lognormal
	<b>CHD</b> <sup>219,246</sup>			<b>Stroke</b> <sup>219,246</sup>		
<b>Male smoker</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35-64	2.6	0.041 <sup>‡</sup>	Lognormal	2.4	0.147 <sup>‡</sup>	Lognormal
65+	1.5	0.073 <sup>‡</sup>	Lognormal	1.5	0.114 <sup>‡</sup>	Lognormal
<b>Female smoker</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35-64	3.2	0.068 <sup>‡</sup>	Lognormal	3.8	0.104 <sup>‡</sup>	Lognormal
65+	1.7	0.031 <sup>‡</sup>	Lognormal	1.6	0.068 <sup>‡</sup>	Lognormal
<b>Male quitter</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35-64	1.6	0.068 <sup>‡</sup>	Lognormal	1.0	0.114 <sup>‡</sup>	Lognormal
65+	1.2	0.044 <sup>‡</sup>	Lognormal	1.0	0.054 <sup>‡</sup>	Lognormal
<b>Female quitter</b>						
18-34	1.0	n/a	Fixed	1.0	n/a	Fixed
35-64	1.4	0.079 <sup>‡</sup>	Lognormal	1.5	0.158 <sup>‡</sup>	Lognormal
65+	1.4	0.038 <sup>‡</sup>	Lognormal	1.2	0.093 <sup>‡</sup>	Lognormal
	<b>MI</b> <sup>205</sup>			<b>Asthma exacerbation</b> <sup>219§</sup>		
<b>Male smoker</b>						
18-34				1.4	0.14 <sup>**</sup>	Lognormal
35-64	2.9	0.29 <sup>**</sup>	Lognormal	1.0	0.10 <sup>**</sup>	Lognormal
65+				1.1	0.11 <sup>**</sup>	Lognormal
<b>Female smoker</b>						
18-34				1.4	0.14 <sup>**</sup>	Lognormal
35-64	3.2	0.32 <sup>**</sup>	Lognormal	1.0	0.10 <sup>**</sup>	Lognormal
65+				1.1	0.11 <sup>**</sup>	Lognormal
<b>Male quitter</b>						
18-34				1.0	0.10 <sup>**</sup>	Lognormal
35-64	1.6	0.16 <sup>**</sup>	Lognormal	1.0	0.10 <sup>**</sup>	Lognormal
65+				1.0	0.10 <sup>**</sup>	Lognormal
<b>Female quitter</b>						

Table A12: Relative risk* of developing chronic conditions						
Health State	RR	SE	Distribution	RR	SE	Distribution
18-34	1.3	0.13 <sup>††</sup>	Lognormal	1.0	0.10 <sup>††</sup>	Lognormal
35-64				1.0	0.10 <sup>††</sup>	Lognormal
65+				1.0	0.10 <sup>††</sup>	Lognormal

‡ Standard errors of regression coefficients ( $\hat{\beta}$ ) in Cox proportional hazards models shown in Thun et al.<sup>246</sup> Standard errors were calculated based on hazard rate estimates and their 95% confidence intervals provided in Thun et al. Probabilistic analyses were conducted around  $\hat{\beta} = \ln(\hat{RR})$ , and the relative risk estimate in each iteration was calculated as  $\exp(\hat{\beta})$ .

† Standard error of  $\ln(RR)$ .

\*Reference category is “never smoker”

\*\*We obtained relative risk of PVD based on information regarding baseline smoking status (percentage of current or former smokers) for those who developed PVD and those with no event (“Healthy” group) reported in Price et al.<sup>248</sup> More specifically, it was reported that there were 64 individuals who developed PVD and there were 1,044 individuals with no event. Moreover, at baseline, the proportions of current or former smokers were 53.1% for those who developed PVD and 30.7% for those with no event. The information can be summarized in the following 2 by 2 table:

Table A13: Calculating Relative Risk of PVD			
Baseline status	PVD	Healthy	Total
Smokers or former smokers	34	321	355
Non-smokers	30	723	753
Total	64	1,044	1,108

Therefore, given the total number of individuals who developed PVD and who did not have any event (“Healthy”), the number of smokers or former smokers who developed PVD was 34 (= 64\*0.531) and the number of non-smokes who developed PVD was 30 (=64-34). Similarly, the number of smokers or quitters who are in “Healthy” group was 321 (=1044\*0.307), and the number of non-smokers in the “Healthy” group was 723. The total number of non-smokers (in PVD and “Healthy” group combined) was 753. Based on these numbers, the relative risk of developing PVD for smokers or former smokers versus non-smokers was 2.4 (= [34/355]/[30/753]). Because the target population of the study was those aged between 55 and 74 years, we assumed that relative risks were same for other age groups. Standard error of the natural log of RR ( $\ln RR$ ) was calculated

as:  $\sqrt{\frac{1}{34} - \frac{1}{34+321} + \frac{1}{30} - \frac{1}{30+723}} = 0.242$ . Probabilistic analysis was conducted around  $\ln RR$ , assuming normal distribution around  $\ln(RR)$ .

\*\*\*Relative risk of 1.13 was reported as an excess risk for current smokers compared with current non-smokers. We assumed that the relative risk was 1.00 for former smokers versus never smokers.

§Relative risks for emergency department visit were considered as proxies of relative risks of asthma exacerbation.<sup>219</sup>

††Standard errors were not reported, therefore they were assumed to be 10% of the estimate.

## APPENDIX 15: CALCULATION OF ALL-CAUSE MORTALITY BY SMOKING STATUS

All-cause mortality rates used in our decision models were based on the 2000-2002 Canadian Life Table.<sup>245</sup> Our economic model considered health state transitions by type of smokers. Therefore, death probabilities by smoking status were calculated so that the mortality of smokers was higher than that of quitters.

### Calculation

All-cause mortality of the Canadian general population, prevalence of smokers, quitters and non-smokers in Canada, and death by type of smokers in the US were available. Because death rates by type of smokers were based on the US population, these rates were calibrated to reflect those for the Canadian population using the following formula:<sup>215</sup>

$$D_{ij} = D_{Sij} * S_{ij} + D_{Qij} * Q_{ij} + D_{NSij} * NS_{ij}$$

Where  $D_{ij}$  is the age- and sex-specific all-cause mortality of the Canadian population ( $i$ : male or female;  $j$ : age in years).  $S_{ij}$ ,  $Q_{ij}$  and  $NS_{ij}$  are prevalence of smokers, quitters and non-smokers in Canada, respectively.  $D_{Sij}$ ,  $D_{Qij}$ , and  $D_{NSij}$  are age- and sex-specific death rates for smokers, quitters, and non-smokers, respectively.

Moreover, odds ratios of death by smoking status for non-smokers ( $OR_{NS}$ ) and quitters ( $OR_Q$ ) (relative to smokers) are:

$$OR_{NS} = \frac{D_{NSij}}{D_{Sij}} \rightarrow D_{NSij} = D_{Sij} * OR_{NS}, \text{ and}$$

$$OR_Q = \frac{D_{Qij}}{D_{Sij}} \rightarrow D_{Qij} = D_{Sij} * OR_Q$$

Rearranging the above two equations and substituting them to the first equation will give us the following:

$$\begin{aligned} D_{ij} &= D_{Sij} * S_{ij} + D_{Sij} * OR_Q * Q_{ij} + D_{Sij} * OR_{NS} * NS_{ij} \\ &= D_{Sij} * [S_{ij} + OR_Q * Q_{ij} + OR_{NS} * NS_{ij}] \end{aligned}$$

i.e.,

$$D_{Sij} = \frac{D_{ij}}{S_{ij} + OR_Q * Q_{ij} + OR_{NS} * NS_{ij}}$$

Once  $D_{Sij}$  is found,  $D_{Qij}$  and  $D_{NSij}$  are obtained as:  $D_{Qij} = D_{Sij} * OR_Q$  and  $D_{NSij} = D_{Sij} * OR_{NS}$ .

Table A14 shows death probabilities by age, sex, and smoking status. As was discussed in the main text, it was found that the model over-predicted mortality for smokers and quitters for those aged 30 years and over. Therefore, all-cause mortality shown in Table A14 for smokers and quitters was assumed to be the same as for those with non-smokers after the age of 30 years.

### Data source

Age- and sex-specific all-cause mortality rates for the Canadian general population [ $D_{ij}$ ] was obtained from the Statistics Canada life table.<sup>245</sup>

Prevalence of smokers [ $S_{ij}$ ], quitters [ $Q_{ij}$ ], and non-smokers [ $NS_{ij}$ ] were obtained from the analysis of the Canadian Community Health Survey 3.1. Public Use Microdata files (Table A15).<sup>252</sup> (See Appendix 16 for detailed methods for calculating prevalence estimates.)

Mortality rates by age, sex, and type of smokers were obtained from Rogers and Powell-Griner,<sup>498</sup> which reported death by smoking status (stratified by light and heavy smokers). Because total number of light and heavy smokers by age group was also provided in the same publication, we calculated death rates for current smokers as a weighted average of death rates of light and heavy smokers (Table A16).

<b>Table A14: All-cause mortality by age, sex and smoking status</b>						
	<b>Male</b>			<b>Female</b>		
<b>Age</b>	<b>SMK (<math>D_{Sij}</math>)</b>	<b>FSMK (<math>D_{Qij}</math>)</b>	<b>NS (<math>D_{NSij}</math>)</b>	<b>SMK (<math>D_{Sij}</math>)</b>	<b>FSMK (<math>D_{Qij}</math>)</b>	<b>NS (<math>D_{NSij}</math>)</b>
18	0.0012	0.0005	0.0006	0.0005	0.0002	0.0003
19	0.0013	0.0005	0.0006	0.0005	0.0002	0.0003
20	0.0013	0.0005	0.0006	0.0005	0.0002	0.0003
21	0.0013	0.0006	0.0006	0.0005	0.0002	0.0003
22	0.0014	0.0006	0.0007	0.0005	0.0002	0.0003
23	0.0014	0.0006	0.0007	0.0005	0.0002	0.0003
24	0.0013	0.0006	0.0006	0.0005	0.0002	0.0003
25	0.0013	0.0005	0.0006	0.0005	0.0002	0.0003
26	0.0013	0.0005	0.0006	0.0005	0.0002	0.0003
27	0.0012	0.0005	0.0006	0.0005	0.0002	0.0003
28	0.0013	0.0005	0.0006	0.0005	0.0002	0.0004
29	0.0013	0.0005	0.0006	0.0005	0.0002	0.0004
30	0.0015	0.0006	0.0007	0.0005	0.0003	0.0004
31	0.0015	0.0006	0.0007	0.0005	0.0004	0.0004
32	0.0016	0.0007	0.0007	0.0006	0.0004	0.0005
33	0.0017	0.0007	0.0008	0.0006	0.0004	0.0005
34	0.0018	0.0007	0.0008	0.0007	0.0005	0.0005
35	0.0017	0.0007	0.0010	0.0007	0.0006	0.0006
36	0.0019	0.0008	0.0009	0.0007	0.0008	0.0005
37	0.0019	0.0011	0.0008	0.0010	0.0008	0.0006
38	0.0020	0.0013	0.0008	0.0012	0.0010	0.0004
39	0.0021	0.0012	0.0010	0.0011	0.0012	0.0004
40	0.0025	0.0011	0.0011	0.0010	0.0011	0.0007
41	0.0027	0.0012	0.0012	0.0011	0.0012	0.0007

**Table A14: All-cause mortality by age, sex and smoking status**

Age	Male			Female		
	SMK (D <sub>Sij</sub> )	FSMK (D <sub>Qij</sub> )	NS (D <sub>NSij</sub> )	SMK (D <sub>Sij</sub> )	FSMK (D <sub>Qij</sub> )	NS (D <sub>NSij</sub> )
42	0.0030	0.0013	0.0013	0.0012	0.0013	0.0008
43	0.0032	0.0014	0.0014	0.0013	0.0014	0.0009
44	0.0035	0.0015	0.0016	0.0014	0.0016	0.0010
45	0.0036	0.0020	0.0015	0.0019	0.0015	0.0011
46	0.0040	0.0022	0.0016	0.0021	0.0016	0.0012
47	0.0044	0.0024	0.0018	0.0023	0.0018	0.0013
48	0.0048	0.0026	0.0019	0.0025	0.0020	0.0014
49	0.0052	0.0029	0.0021	0.0027	0.0022	0.0016
50	0.0054	0.0034	0.0021	0.0033	0.0027	0.0011
51	0.0059	0.0037	0.0023	0.0036	0.0029	0.0012
52	0.0065	0.0041	0.0025	0.0040	0.0032	0.0013
53	0.0072	0.0046	0.0028	0.0044	0.0036	0.0015
54	0.0080	0.0051	0.0031	0.0049	0.0039	0.0016
55	0.0092	0.0053	0.0044	0.0045	0.0050	0.0017
56	0.0102	0.0059	0.0048	0.0050	0.0055	0.0019
57	0.0113	0.0065	0.0054	0.0055	0.0061	0.0021
58	0.0125	0.0072	0.0059	0.0060	0.0066	0.0023
59	0.0138	0.0080	0.0066	0.0065	0.0072	0.0025
60	0.0126	0.0097	0.0071	0.0061	0.0076	0.0033
61	0.0139	0.0108	0.0078	0.0067	0.0083	0.0036
62	0.0154	0.0119	0.0086	0.0073	0.0091	0.0040
63	0.0169	0.0131	0.0095	0.0080	0.0100	0.0044
64	0.0186	0.0144	0.0104	0.0088	0.0110	0.0048
65	0.0244	0.0154	0.0112	0.0131	0.0112	0.0064
66	0.0269	0.0169	0.0123	0.0144	0.0123	0.0070
67	0.0296	0.0187	0.0135	0.0158	0.0135	0.0077
68	0.0326	0.0205	0.0149	0.0174	0.0149	0.0085
69	0.0357	0.0225	0.0163	0.0191	0.0163	0.0093
70	0.0356	0.0244	0.0239	0.0211	0.0177	0.0106
71	0.0391	0.0268	0.0263	0.0233	0.0195	0.0117
72	0.0432	0.0296	0.0291	0.0258	0.0216	0.0130
73	0.0478	0.0327	0.0321	0.0286	0.0239	0.0144
74	0.0526	0.0360	0.0354	0.0316	0.0264	0.0159
75	0.0588	0.0402	0.0395	0.0358	0.0300	0.0180
76	0.0649	0.0444	0.0437	0.0398	0.0333	0.0200
77	0.0719	0.0492	0.0483	0.0445	0.0372	0.0224
78	0.0795	0.0544	0.0535	0.0497	0.0416	0.0250
79	0.0877	0.0600	0.0590	0.0552	0.0462	0.0278
80	0.0974	0.0666	0.0654	0.0642	0.0538	0.0323
81	0.1074	0.0735	0.0722	0.0719	0.0602	0.0362
82	0.1188	0.0813	0.0799	0.0811	0.0679	0.0408
83	0.1310	0.0896	0.0881	0.0919	0.0770	0.0462
84	0.1440	0.0986	0.0968	0.1041	0.0872	0.0524
85	0.1583	0.1083	0.1064	0.1175	0.0983	0.0591
86	0.1745	0.1194	0.1173	0.1318	0.1104	0.0663

<b>Table A14: All-cause mortality by age, sex and smoking status</b>						
	<b>Male</b>			<b>Female</b>		
<b>Age</b>	<b>SMK (D<sub>Sij</sub>)</b>	<b>FSMK (D<sub>Qij</sub>)</b>	<b>NS (D<sub>NSij</sub>)</b>	<b>SMK (D<sub>Sij</sub>)</b>	<b>FSMK (D<sub>Qij</sub>)</b>	<b>NS (D<sub>NSij</sub>)</b>
87	0.1929	0.1320	0.1297	0.1470	0.1231	0.0739
88	0.2134	0.1460	0.1434	0.1631	0.1365	0.0820
89	0.2355	0.1611	0.1583	0.1803	0.1509	0.0907
90	0.2597	0.1777	0.1746	0.1983	0.1660	0.0997
91	0.2867	0.1961	0.1927	0.2170	0.1816	0.1091
92	0.3169	0.2168	0.2130	0.2361	0.1977	0.1188
93	0.3141	0.2149	0.2111	0.2588	0.2167	0.1302
94	0.3394	0.2322	0.2282	0.2830	0.2369	0.1423
95	0.3662	0.2506	0.2462	0.3087	0.2584	0.1553
96	0.3946	0.2700	0.2653	0.3360	0.2812	0.1690
97	0.4246	0.2905	0.2854	0.3648	0.3054	0.1835
98	0.4561	0.3121	0.3066	0.3953	0.3309	0.1988
99	0.4893	0.3348	0.3289	0.4273	0.3577	0.2149

SMK = Smoker; FSMK = Former smoker; NS = Non-smoker

<b>Table A15: Prevalence by age group, sex and type of smoker</b>						
	<b>Male (%)</b>			<b>Female (%)</b>		
<b>Age</b>	<b>Current smokers (S<sub>ij</sub>)</b>	<b>Former smokers (Q<sub>ij</sub>)</b>	<b>Never smoked (NS<sub>ij</sub>)</b>	<b>Current smokers (S<sub>ij</sub>)</b>	<b>Former smokers (Q<sub>ij</sub>)</b>	<b>Never smoked (NS<sub>ij</sub>)</b>
15-17	12.7	13.9	73.5	14.0	15.0	71.0
18-19	27.7	20.0	52.3	22.1	18.4	59.5
20-24	32.5	25.3	42.2	28.4	26.6	45.0
25-29	35.4	30.3	34.3	25.4	31.4	43.2
30-34	28.5	35.6	35.9	21.7	33.8	44.5
35-39	30.4	37.0	32.7	22.9	35.6	41.5
40-44	29.3	40.1	30.6	25.0	37.9	37.1
45-59	27.7	45.9	26.4	24.8	41.3	33.9
50-54	24.4	52.3	23.3	23.3	42.9	33.9
55-59	20.7	59.0	20.3	18.1	45.6	36.3
60-64	19.5	62.8	17.8	16.4	49.5	34.1
65-69	15.3	64.8	19.9	13.4	43.3	43.4
70-74	11.4	67.5	21.1	11.8	43.5	44.8
75-79	8.3	73.7	18.0	9.4	41.8	48.8
80+	6.8	74.6	18.7	5.6	38.7	55.7

Source: Canadian Community Health Survey<sup>252</sup>

<b>Table A16: Death by age, sex and type of smokers (per 1,000)</b>						
	<b>Male</b>			<b>Female</b>		
<b>Age</b>	<b>Current smokers (<math>D_{Sij}</math>)</b>	<b>Former smokers (<math>D_{Qij}</math>)</b>	<b>Never smoked (<math>D_{NSij}</math>)</b>	<b>Current smokers (<math>D_{Sij}</math>)</b>	<b>Former smokers (<math>D_{Qij}</math>)</b>	<b>Never smoked (<math>D_{NSij}</math>)</b>
<29	0.01320	0.00558	0.00634	0.00343	0.00152	0.00248
30-34	0.01348	0.00558	0.00599	0.00402	0.00273	0.00315
35-39	0.01611	0.00652	0.00886	0.00503	0.00423	0.00424
40-44	0.02194	0.00932	0.00979	0.00871	0.00984	0.00603
45-49	0.02874	0.01595	0.01160	0.01280	0.01017	0.00737
50-54	0.05627	0.03551	0.02167	0.03369	0.02720	0.01112
55-59	0.08560	0.04943	0.04066	0.04571	0.05043	0.01738
60-64	0.11730	0.09082	0.06578	0.05904	0.07331	0.03202
65-69	0.19078	0.12028	0.08714	0.10688	0.09140	0.05209
70+	0.26163	0.17901	0.17588	0.16886	0.14136	0.08493

Source: Rogers and Powell-Griner<sup>498</sup>

## APPENDIX 16: METHODS FOR THE ANALYSIS OF THE CANADIAN COMMUNITY HEALTH SURVEY

Data used for estimating age- and sex-specific population by smoking status and utility scores for various health states were obtained from Statistics Canada Canadian Community Health Survey (CCHS) Cycle 3.1 (2005) Public Use Microdata Files (PUMF) data.<sup>252</sup>

CCHS targets Canadians aged 12 and older who are community-dwelling, excluding those living in Indian Reserves or Crown lands, long-term care institutions (e.g., hospitals, nursing homes, rehabilitative institutions), and some remote regions, and those who are full-time members of Canadian Forces. The survey represents approximately 98% of the Canadian population over 12 years old. Data collection of CCHS 3.1 took place from January to December 2005 to obtain self-reported socio-demographic, economic and health-related information (e.g., health status, medication use). General information was collected from one knowledgeable member in each selected dwelling. More in-depth health-related information was collected further from a randomly selected person in the dwelling. Proxy response was allowed only if the respondent was physically or mentally ill and/or incapable of responding to the survey.

### *Data and variables*

In our analyses, CCHS 3.1 PUMF Common and Optional Content Files were used. The Common file contains responses for questions that were asked to respondents in all health regions. Responses regarding Health Utilities Index Mark 3 (HUI3) were included in the Optional Content file. Because HUI3 was considered as one of the optional contents, responses were obtained only from selected health regions.<sup>499</sup> The following **is** a list of variables used in our analyses:

<b>Variables used in analyses<sup>500</sup></b>	<b>Description</b>
ADME_RNO	Sequential record number
DHHEGAGE	Age (5-year age group)
DHHE_SEX	Sex
SMKEDSTY*	Type of smoker
CCCE_121**	Has heart disease
CCCE_91F**	Has chronic obstructive pulmonary disease
HUIZDHSI	Overall HUI3 score
WTSE_M	Sampling weights for Common Content file
WTSE_S1M	Sampling weights for Optional Content file

\* Categories: Daily smoker, Occasional smoker (Former daily smoker), Always an occasional smoker, Former daily smoker, Former occasional smoker, Never smoked. In our analysis, “daily”, “occasional” and “always occasional” smokers were considered as Current smoker; “former daily” and “former occasional” smokers were considered as Quitter.

\*\* These variables are based on a question asking if one has long-term conditions that “...are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional”. [Response option: yes, no, don’t know, refusal, not stated]<sup>501</sup> Then the existence or absence of a series of health states were asked, including “Do you have heart disease?”, “Do you have chronic obstructive pulmonary disease (COPD)?”

## ***Sampling error***

Estimates based on CCHS are subject to sampling error. In presenting descriptive statistics, we used approximate coefficient of variation (CV) tables provided by Statistics Canada<sup>502</sup> to determine the degree of sampling error. Based on the Statistics Canada reporting guideline, any estimates with CV between 16.7 and 33.3 are subject to high sampling variability and any estimates with CV above 33.3 are of unacceptable quality due to extremely high sampling variability. In our results, none of descriptive statistics presented here exceeded the CV of 16.7. In addition, none of our results presented here also had estimates with unweighted (or weighted) frequencies less than 10 (or 30), following a releasing guide by Statistics Canada regarding confidentiality.<sup>499</sup>

## **Section I: Methods for calculating age- and sex- specific prevalence by smoking type**

CCHS 3.1 PUMF Common Content file (n = 132,221) was used to obtain age- and sex-specific population estimates by smoking status. After excluding missing values for the smoking status variable (n=597), the sample was reduced to 131,624 observations. Because the excluded sample was less than 1% of the total sample size, we considered potential selection bias to be minimal. There were no missing data for age and sex variables. Due to confidentiality concerns, only age groups (not age in years) were available in PUMF. Results are shown in Table A15.

## **Section II: Methods for estimating utility scores for “No morbidity”, “CHD” and “COPD health states**

CCHS 3.1 PUMF Optional Content file (n = 32,133) was used to estimate mean utility scores by health states.

### **Section II-1: Estimating utilities for “no morbidity” state**

**Method:** Age, sex and/or smoking-state specific utilities for “no morbidity” state were calculated based on respondents without any chronic conditions. An exclusion of respondents with at least one chronic condition (n = 22,794) reduced the sample size to 9,339 respondents. Respondents with missing HUI3 scores and/or smoking status information were eliminated further (n = 266), resulting in 9,073 respondents that were used in our analyses. There were no missing data for age and sex variables. Preliminary descriptive statistics showed that the overall HUI3 scores were left-skewed, and model diagnostics based on linear regressions of HUI3 on age, sex, and smoking status showed non-normal error distribution (results not shown). Recognizing that the distribution of disutilities (i.e., 1-HUI3) fits a gamma distribution,<sup>236</sup> generalized linear models (distribution = gamma; link function = identity) were used to estimate mean HUI3 disutility scores by age, sex, and/or smoking status. The dependent variable was linearly transformed HUI3 scores [ $HUI_{trans} = (1-HUI3) + 1$ ] and  $HUI_{trans}$  was regressed on age group, sex, and smoking status. First, a full model (main effect, two-way and three way interactions of explanatory variables) was estimated and any non-significant interactions (p>0.001) were eliminated one set of variables at a time using a likelihood ratio test. Goodness of fit for the final model was assessed using a chi-square test with a deviance statistic; a non-significant (p>0.001) chi-square statistic indicates that a model fits the data well.<sup>503</sup> Based on the

most parsimonious model, adjusted means of the transformed HUI3 scores by age, sex, and/or smoking status were obtained and they were back-transformed as:  $\hat{HUI3} = 2 - \hat{HUI}_{trans}$  to obtain predicted utility scores by age, sex, and/or smoking status. CCHS is based on a multistage sampling design with unequal selection probabilities, stratification and clustering. To take account partially of this complex survey design, we used sampling weights to calculate prevalence estimates. However, the use of sampling weights only reflects unequal selection probabilities. Because of confidentiality concerns, detailed survey information was not available in PUMF. Therefore, standard errors were not adjusted for stratification and/or clustering using bootstrapping, Taylor linearization, or other methods.<sup>504</sup> All data analyses were conducted by SAS 9.1.3. Generalized linear models were estimated using PROC GENMOD procedure.<sup>505</sup>

**Results:** The three-way interaction was statistically significant at a 1% level. Therefore, the final model included six sets of explanatory variables: age (16 levels), sex, smoking status (3 levels: current, former or never smokers), age\*sex, age\*smoking status, sex\*smoking status, age\*sex\*smoking status. Stratified mean HUI3 scores by age, sex and smoking status and their standard errors are shown in Appendix 17.

## **Section II-2: Estimating utilities for “CHD” and “COPD” states:**

**Method:** Mean utilities for CHD and COPD were estimated using generalized linear models outlined above, with three sets of explanatory variables: sex, smoking status, chronic condition (3 levels: CHD, COPD or otherwise). We did not consider age stratification because a further stratification by age (in addition to sex and smoking) resulted in frequencies that were too small to be disclosed for most age, sex, and smoking status groups (unweighted counts less than 30<sup>499</sup>).

An exclusion of those with missing data for the overall HUI3 scores, smoking status, or response regarding CHD or COPD (n = 9,604) resulted in the final sample size of n = 22,529.

**Results:** After eliminating statistically non-significant interaction terms (sex\*smoking type\*chronic condition, sex\*chronic condition), the final model was based on five sets of explanatory variables: sex, smoking status, chronic condition, smoking status\*chronic condition, and sex\*smoking status. Adjusted mean HUI3 scores for CHD and COPD by sex and smoking type and their standard errors are shown in Appendix 17.

## APPENDIX 17: UTILITY SCORES FOR HEALTH STATES BY AGE, GENDER AND/OR SMOKING STATUS

Table A18: Utility for no morbidity [Mean (Standard error)] <sup>252*</sup>				
Age	Former smoker		Current smoker	
	Male	Female	Male	Female
20	0.93 (0.007)	0.93 (0.009)	0.90 (0.007)	0.90 (0.010)
30	0.95 (0.006)	0.96 (0.008)	0.94 (0.008)	0.94 (0.011)
40	0.95 (0.006)	0.96 (0.007)	0.94 (0.006)	0.94 (0.009)
50	0.90 (0.007)	0.95 (0.008)	0.94 (0.010)	0.92 (0.012)
60	0.95 (0.010)	0.94 (0.012)	0.90 (0.016)	0.96 (0.022)

Table A19: Utility for TIA* [Mean (Standard error)] <sup>255**</sup>				
Age	Former smoker		Current smoker	
	Male	Female	Male	Female
20	0.93 (0.007)	0.93 (0.010)	0.89 (0.007)	0.90 (0.009)
30	0.95 (0.008)	0.96 (0.011)	0.94 (0.006)	0.94 (0.008)
40	0.95 (0.006)	0.96 (0.009)	0.94 (0.006)	0.93 (0.007)
50	0.90 (0.010)	0.94 (0.012)	0.94 (0.007)	0.92 (0.008)
60	0.95 (0.016)	0.94 (0.022)	0.90 (0.010)	0.96 (0.012)

\*Utility for TIA was 0.55.<sup>255</sup> Because the TIA state usually lasts for about 24 hours (i.e., only one day out of 365 days), the utility score was obtained by the weighted average of utilities for TIA and no morbidity state [= 0.55\*(1/365) + (utility for no morbidity state)\*(364/365)].

\*\*Standard errors were assumed to be the same as that for no morbidity state, given that the utility for TIA state was counted only as 1/365 of the total utilities a patient experiences over one year.

Table A20: Utility for COPD, CHD, post stroke, lung cancer [Mean (Standard error)]				
Health state	Current Smoker		Former smoker	
	Male	Female	Male	Female
COPD <sup>252</sup>	0.68 (0.026)		0.65 (0.018)	
CHD <sup>252</sup>	0.77 (0.014)		0.76 (0.007)	
Lung cancer <sup>256</sup>	0.58 (0.037)	0.67 (0.060)	0.58 (0.037)	0.67 (0.060)

Table A21: Utility for asthma exacerbation [Mean] <sup>252,257*</sup>				
Age	Current smoker		Former smoker	
	Male	Female	Male	Female
20	0.89	0.89	0.92	0.93
30	0.93	0.94	0.94	0.95
40	0.93	0.93	0.95	0.95
50	0.93	0.92	0.89	0.94
60	0.90	0.95	0.95	0.93

\* In Bond et al.,<sup>257</sup> utility for asthma exacerbation was 0.56 (regardless of age, sex, and smoking status), which was a weighted average of utilities for GP managed asthma, ER visit exacerbation, and inpatient exacerbation. Standard errors of utilities for GP managed asthma, ER visit exacerbation, and inpatient exacerbation were used for probabilistic analyses. We assumed that the asthma exacerbation state lasted for one week followed by the utility of no morbidity state. For example, utility for asthma exacerbation state for a 20 year-old male current smoker was estimated as the weighted average of utilities of asthma exacerbation (= 0.56) and no morbidity state (0.90; see table "Utility for no morbidity" above) = 0.56\*(one week / 52 weeks) + 0.90\*(51 weeks / 52 weeks) = 0.89.

## APPENDIX 18: INTERVENTION COSTS FOR ECONOMIC MODELS OTHER THAN THE GENERAL POPULATION

Intervention costs for economic models other than general population (2008 Canadian dollars)*				
Name	Dosage	Duration (number of prescription)	Total cost (using base- case unit cost)**	Source
<b>Cost-effectiveness of adding behavioural intervention</b>				
Nicotine patch	22 mg per day in weeks 1 to 5, then 11 mg per day in week 6 <sup>§</sup>	6 weeks (2)	\$185	Lando et al. <sup>125</sup>
Telephone counselling****	Between 10 to 15 minutes per call	Four telephone counselling sessions by a counsellor	\$19.50 (using a rate at 32.5 cents per minute for 15 minutes) <sup>†</sup>	Lando et al. <sup>125</sup> Canadian Cancer Society <sup>‡</sup>
<b>Cost-effectiveness of paying or co-paying for pharmacological interventions</b>				
NRT (weighted cost of gum, patch, and inhaler) <sup>††</sup>	Standard dosage and duration described in the general population model		\$302	Kaper et al. <sup>195</sup>
Bupropion	Standard dosage and duration described in the general population model		\$196	Kaper et al. <sup>195</sup>
Weighted cost of NRT and bupropion <sup>§§</sup>	---	---	\$246	Kaper et al. <sup>195</sup>
<b>Cost-effectiveness of treating those with cardiovascular or smoking related chronic disease</b>				
NRT gum	2 mg gum, 5 times a day	6 weeks (2)	\$93	Hjalmarson <sup>96</sup>
NRT patch	15 mg per day	3 months (3)	\$367	Tonnesen et al. <sup>121</sup>
NRT inhaler	10 mg inhaler, 8 inhalers per day	3 months (3)	\$620	Tonnesen et al. <sup>121</sup>
Weighted cost of NRT cost (gum, patch, inhaler, and patch+inhaler) <sup>§§§</sup>	---	---	\$529	Hjalmarson <sup>96</sup> Tonnesen et al. <sup>121</sup>
Bupropion	150 mg per day in days 1 to 3, then 150 mg twice daily thereafter	7 weeks (2)	\$116	Tonstad et al. <sup>179</sup>

Intervention costs for economic models other than general population (2008 Canadian dollars)*				
Name	Dosage	Duration (number of prescription)	Total cost (using base- case unit cost)**	Source
<b>Cost-effectiveness of treating hospitalized patients</b>				
NRT patch	7, 14 or 21 mg per day	12 weeks (3)	\$367	Campbell et al. <sup>71</sup>
Bupropion	Standard dosage and duration described in the general population model		\$196	Rigotti et al. <sup>170</sup>

\*Unit costs used in the general population model were applied.

\*\*Consistent with a model for general population, full cost (drug cost, dispensing fee, wholesale mark-ups, inventory allowance) was considered in the base-case analyses. In the deterministic sensitivity analyses, cost to the drug plan was reduced by including patient co-payment.

\*\*\*In Lando et al., the behavioural intervention also included telephone calls to helpline. However, the authors reported that less than 1% of the eligible subjects used the helpline.<sup>125</sup> Therefore the cost of helpline was considered as minimum, thus not considered in the analysis.

§Unit cost for 22 mg and 11 mg are not available in the Alberta formulary. Therefore, unit costs for 22 mg and 11 mg patches were assumed to be same as those for 7, 14 and 21 mg.

† Used as a base-case scenario

†† Weights were calculated using private and public insurance claim data at a national level obtained from Brogan Inc. Based on the claim data, the number of claims for NRT gum, patch and inhaler was 33,457 for gum, 386,396 for patch and 1,023 for inhaler. Therefore, weights were calculated as 7.9%, 91.8% and 0.2%, respectively. (Source: Brogan Inc. Public and Private Drug Plan Databases) Total cost of NRT was calculated using this weight.

Acknowledging the potential uncertainty with respect to the claim data, probabilistic analysis was conducted for this weight using Dirichlet distribution with Dirichlet(33457, 386396, 1023).<sup>236</sup> In Kaper et al., NRT sublingual was subject to reimbursement. However, we did not include sublingual in our analysis because it is not marketed in Canada.

§§ Relative use of NRT and bupropion was obtained from the descriptive statistics in Kaper et al.<sup>195</sup> It was reported that, for intervention and control groups, 29 subjects used NRT (of any type) and 33 subjects used bupropion. Therefore, weights were obtained as 46.8% for NRT and 53.2% for bupropion. Uncertainty around the weight was assessed using beta distribution with alpha = 29 and beta = 33.

§§§ Weights of NRT were based on the sample size reported in Hjalmarson<sup>96</sup> and Tonnesen et al.<sup>121</sup> In Hjalmarson, 106 study subjects received NRT gum. In Tonnesen, the number of subjects who received patch, inhaler or patch+inhaler were 104, 118, and 115, respectively. Therefore, weights of gum, patch, inhaler and patch+inhaler were 0.24, 0.23, 0.27, and 0.36, respectively.

‡ Gail Luciano, Smoker's Helpline, Canadian Cancer Society, Hamilton, ON: personal communication, 2009 September 30.

## APPENDIX 19: ANNUAL DIRECT PER-PATIENT MEDICAL COST

Annual direct per-patient medical cost (2008 Canadian dollars)				
Health state	Total cost	Distribution	Distribution parameters	Source
PVD and AAA	\$2,255	n/a	n/a	n/a
<i>Cost of PVD</i>	\$1,543	Gamma	Mean = \$1,543 SE = \$309 <sup>§</sup>	Cameron and Benett <sup>265</sup>
<i>Cost of AAA</i>	\$21,344	Gamma	Mean = \$21,344 SE = \$2,529	OCCI <sup>266</sup>
<i>Proportion of AAA among total PVD and AAA incidence</i>	0.033	Fixed	n/a	Melton et al., <sup>495</sup> Price et al. <sup>248</sup>
Stroke	\$20,826	Gamma	Mean = \$20,826 SE = \$4,165 <sup>§</sup>	Goeree et al. <sup>263</sup>
Post stroke	\$4,163	Gamma	Mean = \$4,163 SE = \$833 <sup>§</sup>	Goeree et al. <sup>263</sup>
TIA	\$13,724**	Gamma	Mean = \$13,724 SE = \$2,173	Goeree et al. <sup>264</sup>
Post TIA	\$0 (assumed)	Fixed	n/a	n/a
MI	\$10,826	Gamma	Mean = \$10,826 SE = \$2,165 <sup>§</sup>	Goeree et al. <sup>263</sup>
Post MI	\$2,864	Gamma	Mean = \$2,864 SE = \$573 <sup>§</sup>	Goeree et al. <sup>263</sup>
CHD	\$3,429	Gamma	Mean = \$3,429 SE = \$686 <sup>§</sup>	Goeree et al. <sup>263</sup>
COPD	\$2,300	Gamma	Mean = \$2,300 SE = \$460 <sup>§</sup>	Bourbeau et al. <sup>506</sup>
Lung Cancer	\$17,873	Normal***	Mean = \$17,873 SE = \$579	Demeter et al. <sup>268</sup>
Asthma exacerbation (weighted cost)	\$84 <sup>‡</sup>	n/a <sup>†</sup>	n/a	n/a
<i>Probability of medically managed exacerbations managed by GP</i>	0.94	Beta	SE = 0.0005	Bond et al. <sup>257</sup>
<i>Probability of hospital managed exacerbations discharged without admission (i.e. probability of ER visit)</i>	0.93	Beta	SE = 0.0006	Bond et al. <sup>257</sup>
<i>GP managed</i>	\$56	Fixed	n/a	Bond et al. <sup>257</sup>
<i>ER visit</i>	\$261	Fixed	n/a	Bond et al. <sup>257</sup>
<i>Inpatient admission</i>	\$3,541	Gamma	Mean = \$3,541 SE = \$248	Bond et al. <sup>257</sup>

SE = standard error, PVD-AAA = peripheral vascular disease or abdominal aortic aneurysm, TIA = transient ischemic attack, MI = myocardial infarction, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease; n/a = not applicable

\*Total costs associated with PVD-AAA were calculated as the sum of PVD costs and the AAA costs weighted by the probability of AAA incidence over the total PVD and AAA incidence. Costs of AAA were based on the average total cost per case (AAA with or without rupture) retrieved from OCCI case costing database. In 2007-2008, there were 307 acute inpatient and 108 ambulatory care cases reported with total average costs (standard deviation) per case of \$28,643 (\$66,390) and \$594 (\$349) respectively. Total costs included direct costs (nursing [including operating room and ICU], diagnostic imaging, pharmacy and laboratory costs) and indirect costs (e.g., overhead expense, including administration and finance).<sup>266</sup> Therefore, weighted total cost of AAA and its pooled standard error were calculated as:

$$\text{Weighted total cost} = \left(\frac{307}{307+108}\right) * \$28,643 + \left(\frac{108}{307+108}\right) * \$594 = \$21,344$$

$$\text{Pooled standard error} = \frac{\sqrt{(307-1) * (\$66,390)^2 + (108-1) * (\$349)^2}}{\sqrt{307+108}} = \$2,529$$

Then, the total AAA cost was weighted based on the incidence of PVD and AAA. Incidence of PVD was 0.01052, which was based on 1,592 subjects aged between 55 and 74 recruited to the Edinburg Artery Study.<sup>248</sup> Age and sex adjusted incidence of AAA was 36.5 per 100,000 person-years from Melton et al.,<sup>495</sup> a 10 year follow-up study in Rochester, Minnesota. Therefore, the total cost of PVD-AAA was calculated as \$2,259 = \$1,543 + \$21,344\*(0.000365/(0.000365+0.01052)). Uncertainties were assessed around the cost of PVD and the cost of AAA but not for incidences of PVD and AAA due to lack of information.

\*\* In Goeree et al.,<sup>264</sup> total cost of TIA also included costs such as assistive devices or home renovations, lost productivity by patient or caregiver and caregivers. We excluded these costs because these costs were considered outside of direct treatment costs. However, we did not adjust for its standard error accordingly due to lack of information. Our method provided a conservative standard error estimate.

\*\*\* Normal distribution was assumed because solutions under the gamma distribution were not found for many iterations.<sup>236</sup>

‡ Cost of asthma exacerbation was based on a weighted average cost of GP managed asthma exacerbation, ER visit and inpatient costs for the exacerbation. The weights were based on the probability of GP managed exacerbations (0.94) over total exacerbations and the probability of hospital ER visit (0.93) over total exacerbation treated in either ER visit or inpatient basis. Therefore, weighted average costs of asthma exacerbation was calculated as = 0.94\*(\$56) + (1-0.94)\*[0.93\*(\$261) + (1-0.93)\*(\$3541)] = \$84. (The total cost is not exactly the same as that reported in Bond et al.<sup>257</sup> due to rounding)

† Probabilistic analyses associated with asthma exacerbation costs were conducted with respect to uncertainties around probabilities of GP managed exacerbation (0.94) and ER visits (0.93), and inpatient admission cost (\$3,541). GP managed and ER visit costs were based on Ontario Schedule of Fees and Benefits. Therefore, they were considered as fixed.<sup>257</sup>

§ Standard error of the estimate was not available. Therefore, it was assumed to be 20% of its mean.<sup>206</sup>

## APPENDIX 20: DETAILED RESULTS OF ECONOMIC ANALYSIS BY AGE AND GENDER

Table A22: Base-Case Results (Cost and QALYs, Male)						
Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	14.362	\$5,405	---	---	---	---
Bupropion	14.380	\$5,566	0.0178	\$161	\$9,063	\$9,063
Varenicline	14.395	\$5,698	0.0323	\$293	\$9,083	\$9,107
<b>Dominated therapies</b>						
Gum	14.376	\$5,599	0.0131	\$194	\$14,784	Dominated
Patch	14.377	\$5,670	0.0149	\$265	\$17,821	Dominated
Lozenge	14.387	\$5,715	0.0248	\$310	\$12,505	Dominated
Inhaler	14.386	\$6,007	0.0235	\$602	\$25,586	Dominated
<b>Male aged 30 years</b>						
No intervention	13.329	\$8,763	---	---	---	---
Bupropion	13.343	\$8,911	0.0145	\$148	\$10,212	\$10,212
Varenicline	13.355	\$9,032	0.0262	\$269	\$10,236	\$10,265
<b>Dominated therapies</b>						
Gum	13.340	\$8,947	0.0107	\$184	\$17,243	Dominated
Patch	13.341	\$9,017	0.0121	\$254	\$20,975	Dominated
Lozenge	13.349	\$9,054	0.0202	\$291	\$14,441	Dominated
Inhaler	13.348	\$9,347	0.0191	\$584	\$30,518	Dominated
<b>Male aged 40 years</b>						
No intervention	11.537	\$12,083	---	---	---	---
Bupropion	11.557	\$12,216	0.0198	\$133	\$6,700	\$6,700
Varenicline	11.573	\$12,325	0.0359	\$241	\$6,717	\$6,738
<b>Dominated therapies</b>						
Gum	11.552	\$12,256	0.0146	\$173	\$11,836	Dominated
Patch	11.554	\$12,325	0.0166	\$241	\$14,563	Dominated
Lozenge	11.565	\$12,354	0.0276	\$270	\$9,789	Dominated
Inhaler	11.563	\$12,648	0.0262	\$564	\$21,535	Dominated
<b>Male aged 50 years</b>						
No intervention	9.648	\$14,793	---	---	---	---
Bupropion	9.660	\$14,914	0.0120	\$122	\$10,114	\$10,114
Varenicline	9.670	\$15,014	0.0218	\$221	\$10,143	\$10,178
<b>Dominated therapies</b>						
Gum	9.657	\$14,957	0.0089	\$165	\$18,577	Dominated
Patch	9.658	\$15,025	0.0101	\$232	\$23,070	Dominated
Lozenge	9.665	\$15,047	0.0168	\$255	\$15,205	Dominated

**Table A22: Base-Case Results (Cost and QALYs, Male)**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
Inhaler	9.664	\$15,342	0.0159	\$549	\$34,556	Dominated
<b>Male aged 60 years</b>						
No intervention	7.328	\$16,230	---	---	---	---
Bupropion	7.356	\$16,344	0.0275	\$114	\$4,136	\$4,136
Varenicline	7.378	\$16,437	0.0499	\$207	\$4,148	\$4,164
<b>Dominated therapies</b>						
Gum	7.349	\$16,389	0.0203	\$159	\$7,834	Dominated
Patch	7.352	\$16,456	0.0230	\$226	\$9,798	Dominated
Lozenge	7.367	\$16,474	0.0384	\$244	\$6,360	Dominated
Inhaler	7.365	\$16,769	0.0364	\$539	\$14,818	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

**Table A23: Base-Case Results (Cost and QALYs, Female)**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Female aged 20 years</b>						
No intervention	14.644	\$5,734	---	---	---	---
Bupropion	14.661	\$5,894	0.0167	\$160	\$9,579	\$9,579
Varenicline	14.675	\$6,024	0.0303	\$290	\$9,599	\$9,625
<b>Dominated therapies</b>						
Gum	14.657	\$5,926	0.0123	\$193	\$15,677	Dominated
Patch	14.658	\$5,998	0.0140	\$264	\$18,915	Dominated
Lozenge	14.668	\$6,042	0.0233	\$308	\$13,247	Dominated
Inhaler	14.666	\$6,334	0.0221	\$600	\$27,192	Dominated
<b>Female aged 30 years</b>						
No intervention	13.623	\$9,231	---	---	---	---
Bupropion	13.639	\$9,377	0.0160	\$146	\$9,139	\$9,139
Varenicline	13.652	\$9,497	0.0290	\$266	\$9,161	\$9,187
<b>Dominated therapies</b>						
Gum	13.634	\$9,414	0.0118	\$183	\$15,494	Dominated
Patch	13.636	\$9,484	0.0134	\$253	\$18,867	Dominated
Lozenge	13.645	\$9,521	0.0223	\$289	\$12,962	Dominated
Inhaler	13.644	\$9,813	0.0212	\$582	\$27,493	Dominated
<b>Female aged 40 years</b>						
No intervention	11.839	\$12,795	---	---	---	---
Bupropion	11.862	\$12,926	0.0235	\$130	\$5,547	\$5,547
Varenicline	11.881	\$13,032	0.0426	\$237	\$5,562	\$5,580
<b>Dominated therapies</b>						

**Table A23: Base-Case Results (Cost and QALYs, Female)**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
Gum	11.856	\$12,966	0.0173	\$171	\$9,876	Dominated
Patch	11.858	\$13,035	0.0197	\$240	\$12,173	Dominated
Lozenge	11.871	\$13,062	0.0328	\$267	\$8,151	Dominated
Inhaler	11.870	\$13,356	0.0311	\$561	\$18,048	Dominated
<b>Female aged 50 years</b>						
No intervention	10.134	\$15,849	---	---	---	---
Bupropion	10.158	\$15,968	0.0240	\$119	\$4,944	\$4,944
Varenicline	10.178	\$16,065	0.0435	\$216	\$4,958	\$4,976
<b>Dominated therapies</b>						
Gum	10.152	\$16,011	0.0177	\$162	\$9,186	Dominated
Patch	10.154	\$16,079	0.0201	\$230	\$11,439	Dominated
Lozenge	10.168	\$16,100	0.0334	\$251	\$7,496	Dominated
Inhaler	10.166	\$16,395	0.0317	\$545	\$17,198	Dominated
<b>Female aged 60 years</b>						
No intervention	8.509	\$17,583	---	---	---	---
Bupropion	8.527	\$17,694	0.0183	\$111	\$6,058	\$6,058
Varenicline	8.542	\$17,785	0.0333	\$202	\$6,077	\$6,100
<b>Dominated therapies</b>						
Gum	8.523	\$17,740	0.0135	\$157	\$11,606	Dominated
Patch	8.524	\$17,807	0.0154	\$223	\$14,552	Dominated
Lozenge	8.535	\$17,824	0.0256	\$240	\$9,395	Dominated
Inhaler	8.533	\$18,119	0.0243	\$536	\$22,082	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

**Table A24: Base-Case Results (Cost and LYs, Male)**

Intervention	LYs	Cost	Incremental LYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	16.192	\$5,405	---	---	---	---
Bupropion	16.200	\$5,566	0.0084	\$161	\$19,244	\$19,244
Varenicline	16.207	\$5,698	0.0152	\$293	\$19,285	\$19,336
<b>Dominated therapies</b>						
Gum	16.198	\$5,599	0.0062	\$194	\$31,391	Dominated
Patch	16.199	\$5,670	0.0070	\$265	\$37,840	Dominated
Lozenge	16.203	\$5,715	0.0117	\$310	\$26,551	Dominated
Inhaler	16.203	\$6,007	0.0111	\$602	\$54,327	Dominated

**Table A24: Base-Case Results (Cost and LYs, Male)**

Intervention	LYs	Cost	Incremental LYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 30 years</b>						
No intervention	14.671	\$8,763	---	---	---	---
Bupropion	14.682	\$8,911	0.0116	\$148	\$12,738	\$12,738
Varenicline	14.692	\$9,032	0.0210	\$269	\$12,767	\$12,804
<b>Dominated therapies</b>						
Gum	14.679	\$8,947	0.0085	\$184	\$21,507	Dominated
Patch	14.680	\$9,017	0.0097	\$254	\$26,162	Dominated
Lozenge	14.687	\$9,054	0.0162	\$291	\$18,012	Dominated
Inhaler	14.686	\$9,347	0.0153	\$584	\$38,065	Dominated
<b>Male aged 40 years</b>						
No intervention	12.902	\$12,083	---	---	---	---
Bupropion	12.919	\$12,216	0.0165	\$133	\$8,023	\$8,023
Varenicline	12.932	\$12,325	0.0300	\$241	\$8,044	\$8,069
<b>Dominated therapies</b>						
Gum	12.914	\$12,256	0.0122	\$173	\$14,174	Dominated
Patch	12.916	\$12,325	0.0138	\$241	\$17,439	Dominated
Lozenge	12.925	\$12,354	0.0231	\$270	\$11,723	Dominated
Inhaler	12.924	\$12,648	0.0219	\$564	\$25,788	Dominated
<b>Male aged 50 years</b>						
No intervention	10.957	\$14,793	---	---	---	---
Bupropion	10.977	\$14,914	0.0200	\$122	\$6,083	\$6,083
Varenicline	10.994	\$15,014	0.0363	\$221	\$6,100	\$6,122
<b>Dominated therapies</b>						
Gum	10.972	\$14,957	0.0147	\$165	\$11,173	Dominated
Patch	10.974	\$15,025	0.0167	\$232	\$13,875	Dominated
Lozenge	10.985	\$15,047	0.0279	\$255	\$9,145	Dominated
Inhaler	10.984	\$15,342	0.0264	\$549	\$20,784	Dominated
<b>Male aged 60 years</b>						
No intervention	8.681	\$16,230	---	---	---	---
Bupropion	8.703	\$16,344	0.0213	\$114	\$5,351	\$5,351
Varenicline	8.720	\$16,437	0.0386	\$207	\$5,368	\$5,387
<b>Dominated therapies</b>						
Gum	8.697	\$16,389	0.0157	\$159	\$10,137	Dominated
Patch	8.699	\$16,456	0.0178	\$226	\$12,678	Dominated
Lozenge	8.711	\$16,474	0.0296	\$244	\$8,230	Dominated
Inhaler	8.709	\$16,769	0.0281	\$539	\$19,174	Dominated

ICER = incremental cost-effectiveness ratio; LY = life-year; vs. = versus.

**Table A25: Base-Case Results (Cost and LYs, Female)**

Intervention	LYs	Cost	Incremental LYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Female aged 20 years</b>						
No intervention	16.455	\$5,734	---	---	---	---
Bupropion	16.463	\$5,894	0.0075	\$160	\$21,238	\$21,238
Varenicline	16.469	\$6,024	0.0136	\$290	\$21,283	\$21,340
<b>Dominated therapies</b>						
Gum	16.461	\$5,926	0.0055	\$193	\$34,759	Dominated
Patch	16.462	\$5,998	0.0063	\$264	\$41,936	Dominated
Lozenge	16.466	\$6,042	0.0105	\$308	\$29,371	Dominated
Inhaler	16.465	\$6,334	0.0100	\$600	\$60,289	Dominated
<b>Female aged 30 years</b>						
No intervention	14.939	\$9,231	---	---	---	---
Bupropion	14.951	\$9,377	0.0121	\$146	\$12,100	\$12,100
Varenicline	14.961	\$9,497	0.0219	\$266	\$12,129	\$12,164
<b>Dominated therapies</b>						
Gum	14.948	\$9,414	0.0089	\$183	\$20,514	Dominated
Patch	14.949	\$9,484	0.0101	\$253	\$24,980	Dominated
Lozenge	14.956	\$9,521	0.0169	\$289	\$17,161	Dominated
Inhaler	14.955	\$9,813	0.0160	\$582	\$36,400	Dominated
<b>Female aged 40 years</b>						
No intervention	13.323	\$12,795	---	---	---	---
Bupropion	13.340	\$12,926	0.0172	\$130	\$7,599	\$7,599
Varenicline	13.354	\$13,032	0.0311	\$237	\$7,619	\$7,643
<b>Dominated therapies</b>						
Gum	13.335	\$12,966	0.0126	\$171	\$13,528	Dominated
Patch	13.337	\$13,035	0.0144	\$240	\$16,676	Dominated
Lozenge	13.347	\$13,062	0.0239	\$267	\$11,165	Dominated
Inhaler	13.345	\$13,356	0.0227	\$561	\$24,724	Dominated
<b>Female aged 50 years</b>						
No intervention	11.681	\$15,849	---	---	---	---
Bupropion	11.702	\$15,968	0.0204	\$119	\$5,806	\$5,806
Varenicline	11.718	\$16,065	0.0370	\$216	\$5,823	\$5,844
<b>Dominated therapies</b>						
Gum	11.696	\$16,011	0.0150	\$162	\$10,789	Dominated
Patch	11.698	\$16,079	0.0171	\$230	\$13,435	Dominated
Lozenge	11.710	\$16,100	0.0285	\$251	\$8,804	Dominated
Inhaler	11.708	\$16,395	0.0270	\$545	\$20,198	Dominated
<b>Female aged 60 years</b>						
No intervention	9.711	\$17,583	---	---	---	---
Bupropion	9.732	\$17,694	0.0217	\$111	\$5,132	\$5,132

**Table A25: Base-Case Results (Cost and LYs, Female)**

Intervention	LYs	Cost	Incremental LYs (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
Varenicline	9.750	\$17,785	0.0393	\$202	\$5,148	\$5,167
<b>Dominated therapies</b>						
Gum	9.727	\$17,740	0.0159	\$157	\$9,832	Dominated
Patch	9.729	\$17,807	0.0181	\$223	\$12,327	Dominated
Lozenge	9.741	\$17,824	0.0302	\$240	\$7,959	Dominated
Inhaler	9.739	\$18,119	0.0286	\$536	\$18,706	Dominated

ICER = incremental cost-effectiveness ratio; LY = life-year; vs. = versus.

**Table A26: Base-Case Results (Cost and Quitters, Male)\***

Intervention	Total Quitters (per 1,000 smokers)	Total Cost (per 1,000 smokers) <sup>†</sup>	Incremental Quitters (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	34	\$20	---	---	---	---
Bupropion	64	\$12,497	30	\$12,477	\$421	\$421
Varenicline	88	\$31,259	54	\$31,238	\$582	\$779
<b>Dominated therapies</b>						
Gum	56	\$12,700	22	\$12,680	\$581	Dominated
Patch	59	\$18,125	25	\$18,105	\$730	Dominated
Lozenge	75	\$27,691	41	\$27,671	\$670	Dominated
Inhaler	73	\$50,344	39	\$50,324	\$1,285	Dominated
<b>Male aged 30 years</b>						
No intervention	34	\$660	---	---	---	---
Bupropion	64	\$13,685	30	\$13,026	\$440	\$440
Varenicline	88	\$32,888	54	\$32,228	\$601	\$798
<b>Dominated therapies</b>						
Gum	56	\$13,742	22	\$13,082	\$600	Dominated
Patch	59	\$19,219	25	\$18,559	\$749	Dominated
Lozenge	75	\$29,090	41	\$28,430	\$689	Dominated
Inhaler	73	\$51,688	39	\$51,028	\$1,304	Dominated
<b>Male aged 40 years</b>						
No intervention	34	\$3,178	---	---	---	---
Bupropion	64	\$18,486	30	\$15,308	\$509	\$509
Varenicline	88	\$39,610	54	\$36,431	\$671	\$871
<b>Dominated therapies</b>						

**Table A26: Base-Case Results (Cost and Quitters, Male)\***

Intervention	Total Quitters (per 1,000 smokers)	Total Cost (per 1,000 smokers) <sup>†</sup>	Incremental Quitters (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
Gum	56	\$17,967	22	\$14,789	\$666	Dominated
Patch	59	\$23,705	25	\$20,526	\$815	Dominated
Lozenge	76	\$34,867	42	\$31,688	\$758	Dominated
Inhaler	74	\$57,475	40	\$54,296	\$1,369	Dominated
<b>Male aged 50 years</b>						
No intervention	34	\$6,894	---	---	---	---
Bupropion	64	\$25,514	30	\$18,620	\$611	\$611
Varenicline	89	\$49,387	55	\$42,493	\$775	\$979
<b>Dominated therapies</b>						
Gum	57	\$24,145	23	\$17,251	\$764	Dominated
Patch	60	\$30,241	26	\$23,348	\$913	Dominated
Lozenge	76	\$43,266	42	\$36,373	\$860	Dominated
Inhaler	74	\$65,787	40	\$58,893	\$1,467	Dominated
<b>Male aged 60 years</b>						
No intervention	34	\$13,524	---	---	---	---
Bupropion	65	\$38,040	31	\$24,517	\$788	\$788
Varenicline	90	\$66,799	56	\$53,275	\$955	\$1,167
<b>Dominated therapies</b>						
Gum	57	\$35,154	23	\$21,630	\$935	Dominated
Patch	60	\$41,886	26	\$28,362	\$1,083	Dominated
Lozenge	77	\$58,224	43	\$44,701	\$1,038	Dominated
Inhaler	75	\$80,564	41	\$67,040	\$1,640	Dominated

ICER = incremental cost-effectiveness ratio; vs. = versus.

\*The analyses are based on a one-year time horizon.

<sup>†</sup>The cost of no intervention is greater than zero. The non-zero costs are those associated with smoking-related disease that will occur during the first cycle.

**Table A27: Base-Case Results (Cost and Quitters, Female)\***

Intervention	Total Quitters (per 1,000 smokers)	Total Cost (per 1,000 smokers) <sup>†</sup>	Incremental Quitters (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Female aged 20 years</b>						
No intervention	34	\$20	---	---	---	---
Bupropion	64	\$12,491	30	\$12,470	\$421	\$421
Varenicline	88	\$31,243	54	\$31,222	\$582	\$779
<b>Dominated therapies</b>						
Gum	56	\$12,693	22	\$12,673	\$581	Dominated
Patch	59	\$18,116	25	\$18,095	\$730	Dominated
Lozenge	75	\$27,677	41	\$27,657	\$670	Dominated
Inhaler	73	\$50,318	39	\$50,298	\$1,285	Dominated
<b>Female aged 30 years</b>						
No intervention	34	\$660	---	---	---	---
Bupropion	64	\$13,685	30	\$13,026	\$440	\$440
Varenicline	88	\$32,888	54	\$32,228	\$601	\$798
<b>Dominated therapies</b>						
Gum	56	\$13,742	22	\$13,082	\$600	Dominated
Patch	59	\$19,219	25	\$18,559	\$749	Dominated
Lozenge	75	\$29,090	41	\$28,430	\$689	Dominated
Inhaler	73	\$51,688	39	\$51,028	\$1,304	Dominated
<b>Female aged 40 years</b>						
No intervention	34	\$3,178	---	---	---	---
Bupropion	64	\$18,486	30	\$15,308	\$509	\$509
Varenicline	88	\$39,610	54	\$36,431	\$671	\$871
<b>Dominated therapies</b>						
Gum	56	\$17,967	22	\$14,789	\$666	Dominated
Patch	59	\$23,705	25	\$20,526	\$815	Dominated
Lozenge	76	\$34,867	42	\$31,688	\$758	Dominated
Inhaler	74	\$57,475	40	\$54,296	\$1,369	Dominated
<b>Female aged 50 years</b>						
No intervention	34	\$6,894	---	---	---	---
Bupropion	64	\$25,514	30	\$18,620	\$611	\$611
Varenicline	89	\$49,387	55	\$42,493	\$775	\$979
<b>Dominated therapies</b>						
Gum	57	\$24,145	23	\$17,251	\$764	Dominated
Patch	60	\$30,241	26	\$23,348	\$913	Dominated

**Table A27: Base-Case Results (Cost and Quitters, Female)\***

Intervention	Total Quitters (per 1,000 smokers)	Total Cost (per 1,000 smokers) <sup>†</sup>	Incremental Quitters (vs. no intervention)	Incremental Cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
Lozenge	76	\$43,266	42	\$36,373	\$860	Dominated
Inhaler	74	\$65,787	40	\$58,893	\$1,467	Dominated
<b>Female aged 60 years</b>						
No intervention	34	\$13,524	---	---	---	---
Bupropion	65	\$38,040	31	\$24,517	\$788	\$788
Varenicline	90	\$66,799	56	\$53,275	\$955	\$1,167
<b>Dominated therapies</b>						
Gum	57	\$35,154	23	\$21,630	\$935	Dominated
Patch	60	\$41,886	26	\$28,362	\$1,083	Dominated
Lozenge	77	\$58,225	43	\$44,701	\$1,038	Dominated
Inhaler	75	\$80,564	41	\$67,040	\$1,640	Dominated

ICER = incremental cost-effectiveness ratio; vs. = versus.

\*The analyses are based on a one-year time horizon.

<sup>†</sup>The cost of no intervention is greater than zero. The non-zero costs are those associated with smoking-related disease that will occur during the first cycle.

## APPENDIX 21: CLINICAL EFFICACY DATA USED FOR SENSITIVITY ANALYSES

Table A28: General population model					
Interventions	Log OR (SE)	Spontaneous quit rate as “no intervention”		Placebo quit rate as “no intervention”	
		RR	Quit rate	RR	Quit rate
<b>Point prevalence abstinence rate at 12 months</b>					
No intervention	1	1	0.082 <sup>§234,235</sup>	1	0.135 (SE = 0.016)
NRT Patch	0.522 (0.160)	1.60	0.131	1.54	0.208
NRT Gum	0.729 (0.157)	1.91	0.156	1.81	0.244
NRT Inhaler	0.938 (0.302)	2.27	0.186	2.11	0.285
NRT Lozenge	1.064 (0.492)	2.51	0.206	2.31	0.311
Bupropion	0.599 (0.112)	1.71	0.140	1.64	0.221
Varenicline	0.900 (0.139)	2.20	0.180	2.05	0.227
<b>Continuous abstinence rate at 6 months</b>					
No intervention	1	1	0.042 <sup>§234</sup>	1	0.115 (SE = 0.010)
NRT Patch	0.784 (0.097)	2.09	0.088	1.93	0.222
NRT Gum	0.808 (0.134)	2.13	0.090	1.96	0.226
NRT Inhaler	0.774 (0.218)	2.07	0.087	1.91	0.220
NRT Lozenge	0.797 (0.219)	2.11	0.089	1.95	0.224
Bupropion	0.703 (0.113)	1.94	0.081	1.81	0.208
Varenicline	0.981 (0.101)	2.49	0.105	2.24	0.257
<b>Point prevalence abstinence rate at 6 months</b>					
No intervention	1	1	0.07 <sup>§234</sup>	1	0.179 (SE = 0.017)
NRT Patch	0.594 (0.111)	1.71	0.120	1.58	0.283
NRT Gum	0.511 (0.116)	1.59	0.111	1.49	0.267
NRT Inhaler	0.986 (0.307)	2.40	0.168	2.06	0.369
NRT Lozenge	0.738 (0.393)	1.94	0.136	1.75	0.313
Bupropion	0.640 (0.076)	1.78	0.125	1.63	0.293
Varenicline	1.001 (0.108)	2.43	0.170	2.08	0.372

<sup>§</sup>For 12-month point prevalence abstinence rate, alpha = 34, beta = (414-34) = 380; for 6-month continuous abstinence rate, alpha = 3, beta = (71-3) = 68; for 6-month point prevalence abstinence rate, alpha = 5; beta = (71-5) = 66.<sup>234</sup>

<b>Table A29: Adding behavioural interventions</b>			
<b>Interventions</b>	<b>Log OR (SE)</b>	<b>RR*</b>	<b>Quit rate</b>
<b>Continuous abstinence rate at 6 months</b>			
NRT Patch	1	1	0.150
NRT Patch + Behaviour	0.150 (0.261)	1.13	0.170

\*RR was calculated based on the following formula:  $RR = \frac{e^{\ln OR}}{(1 - p_0) + (p_0) * (e^{\ln OR})}$ , where  $p_0$  refers to a quit rate for “NRT patch” strategy reported above.<sup>206</sup>

<b>Table A30: Cardiovascular or smoking-related diseases</b>			
<b>Interventions</b>	<b>Log OR (SE)</b>	<b>RR**</b>	<b>Quit rate</b>
<b>Placebo quit rate as “no intervention”</b>			
<b>Continuous abstinence at 6 months</b>			
No intervention	1	1	0.127 (SE = 0.074)
NRT*	0.680 (0.691)	1.76	0.223
Bupropion	1.128 (0.957)	2.44	0.310

\*Gum, patch and/or inhaler

\*\*RR was calculated based on the following formula:  $RR = \frac{e^{\ln OR}}{(1 - p_0) + (p_0) * (e^{\ln OR})}$ , where  $p_0$  refers to a quit rate for “no intervention” strategy reported above.<sup>206</sup>

## APPENDIX 22: SENSITIVITY ANALYSES FOR GENERAL POPULATION MODEL

<b>Table A31: Sensitivity analyses of 30% patient co-payment [Cost and QALYs]</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male aged 20 years</b>						
No intervention	14.362	\$5,405	---	---	---	---
Bupropion	14.380	\$5,513	0.0178	\$108	\$6,068	\$6,068
Varenicline	14.395	\$5,620	0.0323	\$216	\$6,683	\$7,438
<b>Dominated therapies</b>						
Gum	14.376	\$5,537	0.0131	\$132	\$10,072	Dominated
Patch	14.377	\$5,608	0.0149	\$203	\$13,619	Dominated
Lozenge	14.387	\$5,651	0.0248	\$246	\$9,930	Dominated
Inhaler	14.386	\$5,939	0.0235	\$534	\$22,694	Dominated
<b>Male aged 40 years</b>						
No intervention	11.537	\$12,083	---	---	---	---
Bupropion	11.557	\$12,163	0.0198	\$79	\$4,010	\$4,010
Varenicline	11.573	\$12,247	0.0359	\$164	\$4,562	\$5,240
<b>Dominated therapies</b>						
Gum	11.552	\$12,194	0.0146	\$111	\$7,605	Dominated
Patch	11.554	\$12,262	0.0166	\$179	\$10,790	Dominated
Lozenge	11.565	\$12,290	0.0276	\$207	\$7,477	Dominated
Inhaler	11.563	\$12,580	0.0262	\$496	\$18,938	Dominated
<b>Female aged 20 years</b>						
No intervention	14.644	\$5,734	---	---	---	---
Bupropion	14.661	\$5,840	0.0167	\$107	\$6,385	\$6,385
Varenicline	14.675	\$5,947	0.0303	\$213	\$7,041	\$7,846
<b>Dominated therapies</b>						
Gum	14.657	\$5,865	0.0123	\$131	\$10,654	Dominated
Patch	14.658	\$5,935	0.014	\$202	\$14,435	Dominated
Lozenge	14.668	\$5,978	0.0233	\$244	\$10,502	Dominated
Inhaler	14.666	\$6,266	0.0221	\$532	\$24,109	Dominated
<b>Female aged 40 years</b>						
No intervention	11.839	\$12,795	---	---	---	---
Bupropion	11.862	\$12,872	0.0235	\$77	\$3,281	\$3,281
Varenicline	11.881	\$12,955	0.0426	\$160	\$3,746	\$4,317
<b>Dominated therapies</b>						
Gum	11.856	\$12,904	0.0173	\$109	\$6,310	Dominated
Patch	11.858	\$12,972	0.0197	\$177	\$8,994	Dominated
Lozenge	11.871	\$12,998	0.0328	\$203	\$6,203	Dominated
Inhaler	11.870	\$13,288	0.0311	\$493	\$15,860	Dominated

**Table A32: Sensitivity analyses of low patch price [Cost and QALYs]**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	14.362	\$5,405	---	---	---	---
Bupropion	14.380	\$5,566	0.0178	\$161	\$9,063	\$9,063
Varenicline	14.395	\$5,698	0.0323	\$293	\$9,083	\$9,107
<b>Dominated therapies</b>						
Gum	14.376	\$5,599	0.0131	\$194	\$14,784	Dominated
Patch	14.377	\$5,616	0.0149	\$211	\$14,160	Dominated
Lozenge	14.387	\$5,715	0.0248	\$310	\$12,505	Dominated
Inhaler	14.386	\$6,007	0.0235	\$602	\$25,586	Dominated
<b>Male aged 40 years</b>						
No intervention	11.537	\$12,083	---	---	---	---
Bupropion	11.557	\$12,216	0.0198	\$133	\$6,700	\$6,700
Varenicline	11.573	\$12,325	0.0359	\$241	\$6,717	\$6,738
<b>Dominated therapies</b>						
Gum	11.552	\$12,256	0.0146	\$173	\$11,836	Dominated
Patch	11.554	\$12,270	0.0166	\$187	\$11,276	Dominated
Lozenge	11.565	\$12,354	0.0276	\$270	\$9,789	Dominated
Inhaler	11.563	\$12,648	0.0262	\$564	\$21,535	Dominated
<b>Female aged 20 years</b>						
No intervention	14.644	\$5,734	---	---	---	---
Bupropion	14.661	\$5,894	0.0167	\$160	\$9,579	\$9,579
Varenicline	14.675	\$6,024	0.0303	\$290	\$9,599	\$9,625
<b>Dominated therapies</b>						
Gum	14.657	\$5,926	0.0123	\$193	\$15,677	Dominated
Patch	14.658	\$5,943	0.0140	\$210	\$15,012	Dominated
Lozenge	14.668	\$6,042	0.0233	\$308	\$13,247	Dominated
Inhaler	14.666	\$6,334	0.0221	\$600	\$27,192	Dominated
<b>Female aged 40 years</b>						
No intervention	11.839	\$12,795	---	---	---	---
Bupropion	11.862	\$12,926	0.0235	\$130	\$5,547	\$5,547
Varenicline	11.881	\$13,032	0.0426	\$237	\$5,562	\$5,580
<b>Dominated therapies</b>						
Gum	11.856	\$12,966	0.0173	\$171	\$9,876	Dominated
Patch	11.858	\$12,980	0.0197	\$185	\$9,404	Dominated
Lozenge	11.871	\$13,062	0.0328	\$267	\$8,151	Dominated
Inhaler	11.870	\$13,356	0.0311	\$561	\$18,048	Dominated

<b>Table A33: Sensitivity analyses of 3% discount rate [Cost and QALYs]</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male aged 20 years</b>						
No intervention	19.919	\$11,020	---	---	---	---
Bupropion	19.949	\$11,179	0.0302	\$158	\$5,247	\$5,247
Varenicline	19.974	\$11,308	0.0547	\$288	\$5,258	\$5,273
<b>Dominated therapies</b>						
Gum	19.942	\$11,215	0.0222	\$194	\$8,753	Dominated
Patch	19.945	\$11,288	0.0252	\$268	\$10,614	Dominated
Lozenge	19.961	\$11,330	0.0421	\$309	\$7,356	Dominated
Inhaler	19.959	\$11,633	0.0399	\$613	\$15,373	Dominated
<b>Male aged 40 years</b>						
No intervention	14.691	\$18,075	---	---	---	---
Bupropion	14.722	\$18,207	0.0315	\$131	\$4,171	\$4,171
Varenicline	14.748	\$18,314	0.0570	\$239	\$4,182	\$4,196
<b>Dominated therapies</b>						
Gum	14.714	\$18,250	0.0232	\$175	\$7,533	Dominated
Patch	14.717	\$18,321	0.0263	\$245	\$9,318	Dominated
Lozenge	14.735	\$18,347	0.0439	\$272	\$6,193	Dominated
Inhaler	14.732	\$18,653	0.0416	\$577	\$13,881	Dominated
<b>Female aged 20 years</b>						
No intervention	20.470	\$11,889	---	---	---	---
Bupropion	20.499	\$12,044	0.0292	\$156	\$5,324	\$5,324
Varenicline	20.523	\$12,172	0.0530	\$283	\$5,336	\$5,351
<b>Dominated therapies</b>						
Gum	20.492	\$12,081	0.0215	\$193	\$8,939	Dominated
Patch	20.494	\$12,155	0.0245	\$266	\$10,859	Dominated
Lozenge	20.511	\$12,195	0.0408	\$306	\$7,499	Dominated
Inhaler	20.509	\$12,499	0.0387	\$610	\$15,766	Dominated
<b>Female aged 40 years</b>						
No intervention	15.266	\$19,477	---	---	---	---
Bupropion	15.303	\$19,606	0.0370	\$128	\$3,468	\$3,468
Varenicline	15.333	\$19,710	0.0670	\$233	\$3,477	\$3,489
<b>Dominated therapies</b>						
Gum	15.293	\$19,650	0.0272	\$172	\$6,328	Dominated
Patch	15.297	\$19,720	0.0309	\$243	\$7,847	Dominated
Lozenge	15.317	\$19,745	0.0515	\$267	\$5,188	Dominated
Inhaler	15.315	\$20,051	0.0489	\$573	\$11,729	Dominated

<b>Table A34: Sensitivity analyses of 0% discount rate [Cost and QALYs]</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male aged 20 years</b>						
No intervention	37.364	\$36,392	---	---	---	---
Bupropion	37.450	\$36,550	0.0862	\$158	\$1,830	\$1,830
Varenicline	37.521	\$36,679	0.1564	\$287	\$1,835	\$1,840
<b>Dominated therapies</b>						
Gum	37.428	\$36,591	0.0635	\$199	\$3,131	Dominated
Patch	37.436	\$36,668	0.0722	\$276	\$3,822	Dominated
Lozenge	37.484	\$36,707	0.1203	\$314	\$2,613	Dominated
Inhaler	37.478	\$37,030	0.1140	\$637	\$5,587	Dominated
<b>Male aged 40 years</b>						
No intervention	22.653	\$36,061	---	---	---	---
Bupropion	22.723	\$36,204	0.0701	\$143	\$2,038	\$2,038
Varenicline	22.780	\$36,321	0.1272	\$260	\$2,043	\$2,050
<b>Dominated therapies</b>						
Gum	22.705	\$36,249	0.0517	\$188	\$3,638	Dominated
Patch	22.712	\$36,324	0.0587	\$263	\$4,487	Dominated
Lozenge	22.751	\$36,354	0.0978	\$293	\$3,000	Dominated
Inhaler	22.746	\$36,678	0.0927	\$618	\$6,658	Dominated
<b>Female aged 20 years</b>						
No intervention	39.357	\$40,792	---	---	---	---
Bupropion	39.447	\$40,947	0.0901	\$155	\$1,715	\$1,715
Varenicline	39.520	\$41,073	0.1634	\$281	\$1,720	\$1,725
<b>Dominated therapies</b>						
Gum	39.423	\$40,989	0.0664	\$196	\$2,960	Dominated
Patch	39.432	\$41,065	0.0754	\$273	\$3,621	Dominated
Lozenge	39.482	\$41,102	0.1256	\$310	\$2,464	Dominated
Inhaler	39.476	\$41,425	0.1191	\$633	\$5,312	Dominated
<b>Female aged 40 years</b>						
No intervention	24.284	\$40,392	---	---	---	---
Bupropion	24.367	\$40,534	0.0834	\$142	\$1,700	\$1,700
Varenicline	24.435	\$40,650	0.1512	\$258	\$1,705	\$1,711
<b>Dominated therapies</b>						
Gum	24.345	\$40,579	0.0614	\$187	\$3,046	Dominated
Patch	24.353	\$40,655	0.0698	\$262	\$3,760	Dominated
Lozenge	24.400	\$40,684	0.1163	\$292	\$2,510	Dominated
Inhaler	24.394	\$41,008	0.1103	\$616	\$5,586	Dominated

<b>Table A35: Sensitivity analyses of low dosage of gum and lozenge [Cost and QALYs]</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male aged 20 years</b>						
No intervention	14.362	\$5,405	---	---	---	---
Bupropion	14.380	\$5,566	0.0178	\$161	\$9,063	\$9,063
Varenicline	14.395	\$5,698	0.0323	\$293	\$9,083	\$9,107
<b>Dominated therapies</b>						
Gum	14.376	\$5,568	0.0131	\$163	\$12,436	Dominated
Patch	14.377	\$5,670	0.0149	\$265	\$17,821	Dominated
Lozenge	14.387	\$5,679	0.0248	\$274	\$11,038	Dominated
Inhaler	14.386	\$6,007	0.0235	\$602	\$25,586	Dominated
<b>Male aged 40 years</b>						
No intervention	11.537	\$12,083	---	---	---	---
Bupropion	11.557	\$12,216	0.0198	\$133	\$6,700	\$6,700
Varenicline	11.573	\$12,325	0.0359	\$241	\$6,717	\$6,738
<b>Dominated therapies</b>						
Gum	11.552	\$12,225	0.0146	\$142	\$9,727	Dominated
Lozenge	11.565	\$12,317	0.0276	\$234	\$8,473	Dominated
Patch	11.554	\$12,325	0.0166	\$241	\$14,563	Dominated
Inhaler	11.563	\$12,648	0.0262	\$564	\$21,535	Dominated
<b>Female aged 20 years</b>						
No intervention	14.644	\$5,734	---	---	---	---
Bupropion	14.661	\$5,894	0.0167	\$160	\$9,579	\$9,579
Varenicline	14.675	\$6,024	0.0303	\$290	\$9,599	\$9,625
<b>Dominated therapies</b>						
Gum	14.657	\$5,896	0.0123	\$162	\$13,174	Dominated
Patch	14.658	\$5,998	0.0140	\$264	\$18,915	Dominated
Lozenge	14.668	\$6,006	0.0233	\$272	\$11,684	Dominated
Inhaler	14.666	\$6,334	0.0221	\$600	\$27,192	Dominated
<b>Female aged 40 years</b>						
No intervention	11.839	\$12,795	---	---	---	---
Bupropion	11.862	\$12,926	0.0235	\$130	\$5,547	\$5,547
Varenicline	11.881	\$13,032	0.0426	\$237	\$5,562	\$5,580
<b>Dominated therapies</b>						
Gum	11.856	\$12,935	0.0173	\$140	\$8,099	Dominated
Lozenge	11.871	\$13,026	0.0328	\$231	\$7,041	Dominated
Patch	11.858	\$13,035	0.0197	\$240	\$12,173	Dominated
Inhaler	11.870	\$13,356	0.0311	\$561	\$18,048	Dominated

**Table A36: Sensitivity analyses of using placebo quit rate (CAR at 1 year)  
[Cost and QALYs]**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	14.401	\$5,369	---	---	---	---
Bupropion	14.446	\$5,505	0.0453	\$136	\$3,002	\$3,002
Varenicline	14.480	\$5,620	0.0786	\$250	\$3,184	\$3,431
<b>Dominated therapies</b>						
Gum	14.435	\$5,544	0.0338	\$175	\$5,161	Dominated
Patch	14.439	\$5,613	0.0382	\$244	\$6,378	Dominated
Lozenge	14.463	\$5,645	0.0618	\$276	\$4,468	Dominated
Inhaler	14.460	\$5,939	0.0588	\$569	\$9,678	Dominated
<b>Male aged 40 years</b>						
No intervention	11.580	\$11,986	---	---	---	---
Bupropion	11.630	\$12,050	0.0504	\$63	\$1,257	\$1,257
Varenicline	11.668	\$12,111	0.0875	\$124	\$1,421	\$1,642
<b>Dominated therapies</b>						
Gum	11.618	\$12,107	0.0377	\$120	\$3,196	Dominated
Lozenge	11.649	\$12,163	0.0688	\$177	\$2,573	Dominated
Patch	11.623	\$12,169	0.0426	\$183	\$4,289	Dominated
Inhaler	11.646	\$12,461	0.0655	\$475	\$7,251	Dominated
<b>Female aged 20 years</b>						
No intervention	14.680	\$5,695	---	---	---	---
Bupropion	14.723	\$5,828	0.0425	\$132	\$3,117	\$3,117
Varenicline	14.754	\$5,939	0.0737	\$244	\$3,311	\$3,574
<b>Dominated therapies</b>						
Gum	14.712	\$5,867	0.0317	\$172	\$5,419	Dominated
Patch	14.716	\$5,936	0.0359	\$241	\$6,716	Dominated
Lozenge	14.738	\$5,967	0.0580	\$271	\$4,680	Dominated
Inhaler	14.736	\$6,260	0.0552	\$565	\$10,234	Dominated
<b>Female aged 40 years</b>						
No intervention	11.889	\$12,693	---	---	---	---
Bupropion	11.949	\$12,750	0.0598	\$57	\$961	\$961
Varenicline	11.993	\$12,807	0.1039	\$114	\$1,099	\$1,285
<b>Dominated therapies</b>						
Gum	11.934	\$12,809	0.0447	\$116	\$2,595	Dominated
Lozenge	11.971	\$12,862	0.0817	\$169	\$2,070	Dominated
Patch	11.940	\$12,871	0.0505	\$178	\$3,515	Dominated
Inhaler	11.967	\$13,160	0.0777	\$467	\$6,012	Dominated

**Table A37: Sensitivity analyses of using PPA at 1 year as the definition of quit rate  
[Cost and QALYs]**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	14.391	\$5,378	---	---	---	---
Lozenge	14.466	\$5,643	0.0743	\$264	\$3,557	\$3,557
<b>Dominated therapies</b>						
Bupropion	14.426	\$5,524	0.0348	\$146	\$4,183	Dominated
Gum	14.436	\$5,543	0.0446	\$165	\$3,687	Dominated
Patch	14.421	\$5,630	0.0294	\$252	\$8,577	Dominated
Varenicline	14.450	\$5,647	0.0590	\$268	\$4,547	Dominated
Inhaler	14.454	\$5,944	0.0624	\$566	\$9,066	Dominated
<b>Male aged 40 years</b>						
No intervention	11.569	\$12,011	---	---	---	---
Lozenge	11.652	\$12,156	0.0828	\$145	\$1,756	\$1,756
<b>Dominated therapies</b>						
Bupropion	11.608	\$12,100	0.0388	\$90	\$2,317	Dominated
Gum	11.619	\$12,104	0.0497	\$93	\$1,873	Dominated
Varenicline	11.635	\$12,184	0.0657	\$174	\$2,644	Dominated
Patch	11.602	\$12,215	0.0327	\$205	\$6,263	Dominated
Inhaler	11.639	\$12,477	0.0695	\$466	\$6,702	Dominated
<b>Female aged 20 years</b>						
No intervention	14.671	\$5,705	---	---	---	---
Lozenge	14.741	\$5,964	0.0697	\$259	\$3,709	\$3,709
<b>Dominated therapies</b>						
Bupropion	14.704	\$5,848	0.0326	\$143	\$4,376	Dominated
Gum	14.713	\$5,866	0.0419	\$161	\$3,848	Dominated
Patch	14.699	\$5,955	0.0276	\$250	\$9,060	Dominated
Varenicline	14.727	\$5,969	0.0554	\$264	\$4,764	Dominated
Inhaler	14.730	\$6,266	0.0586	\$561	\$9,582	Dominated
<b>Female aged 40 years</b>						
No intervention	11.877	\$12,718	---	---	---	---
Lozenge	11.975	\$12,854	0.0983	\$136	\$1,381	\$1,381
<b>Dominated therapies</b>						
Bupropion	11.923	\$12,804	0.0460	\$85	\$1,854	Dominated
Gum	11.936	\$12,806	0.0590	\$87	\$1,479	Dominated
Varenicline	11.955	\$12,885	0.0780	\$166	\$2,130	Dominated
Patch	11.916	\$12,920	0.0388	\$201	\$5,179	Dominated
Inhaler	11.959	\$13,176	0.0825	\$458	\$5,549	Dominated

**Table A38: Sensitivity analyses of using PPA at 6 months as the definition of quit rate [Cost and QALYs]**

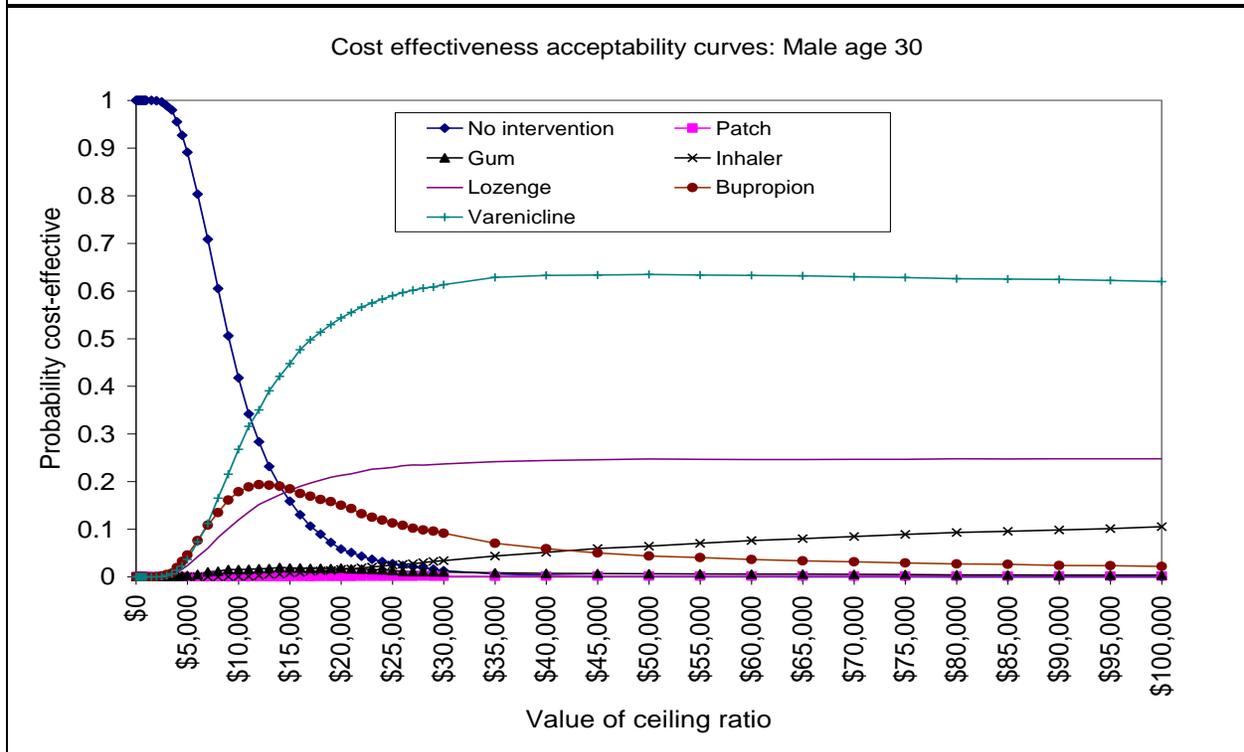
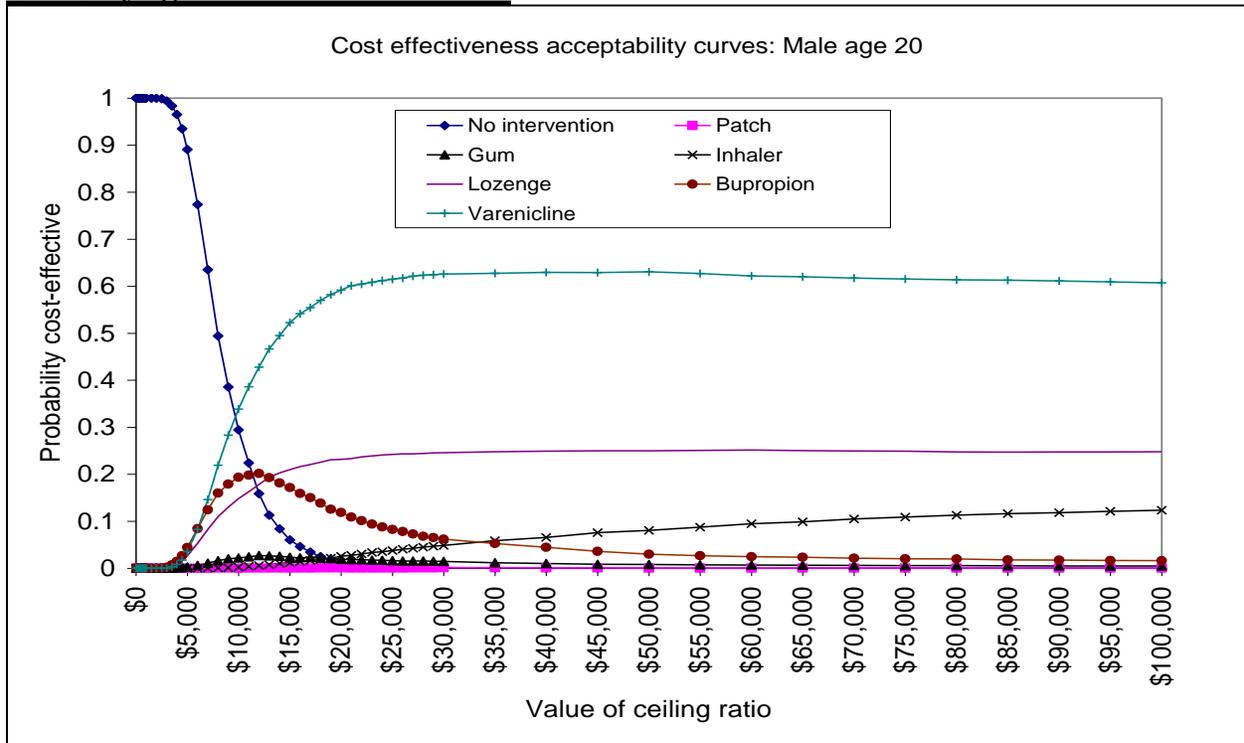
Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	14.389	\$5,382	---	---	---	---
Varenicline	14.455	\$5,678	0.0665	\$296	\$4,452	\$4,452
<b>Dominated therapies</b>						
Bupropion	14.425	\$5,545	0.0365	\$163	\$4,464	Dominated
Gum	14.416	\$5,584	0.0276	\$202	\$7,327	Dominated
Patch	14.422	\$5,660	0.0332	\$278	\$8,360	Dominated
Lozenge	14.432	\$5,709	0.0439	\$328	\$7,464	Dominated
Inhaler	14.454	\$6,011	0.0651	\$629	\$9,664	Dominated
<b>Male aged 40 years</b>						
No intervention	11.569	\$12,012	---	---	---	---
Varenicline	11.646	\$12,190	0.0772	\$178	\$2,311	\$2,311
<b>Dominated therapies</b>						
Bupropion	11.611	\$12,110	0.0424	\$98	\$2,320	Dominated
Gum	11.601	\$12,165	0.0320	\$153	\$4,785	Dominated
Patch	11.607	\$12,231	0.0386	\$219	\$5,674	Dominated
Lozenge	11.620	\$12,262	0.0510	\$250	\$4,903	Dominated
Inhaler	11.644	\$12,526	0.0756	\$514	\$6,796	Dominated
<b>Female aged 20 years</b>						
No intervention	14.668	\$5,709	---	---	---	---
Varenicline	14.730	\$5,999	0.0617	\$291	\$4,710	\$4,710
<b>Dominated therapies</b>						
Bupropion	14.702	\$5,869	0.0339	\$160	\$4,722	Dominated
Gum	14.694	\$5,908	0.0256	\$200	\$7,807	Dominated
Patch	14.699	\$5,984	0.0308	\$275	\$8,921	Dominated
Lozenge	14.709	\$6,033	0.0407	\$324	\$7,955	Dominated
Inhaler	14.729	\$6,332	0.0604	\$624	\$10,325	Dominated
<b>Female aged 40 years</b>						
No intervention	11.875	\$12,720	---	---	---	---
Varenicline	11.966	\$12,890	0.0910	\$170	\$1,869	\$1,869
<b>Dominated therapies</b>						
Bupropion	11.925	\$12,814	0.0500	\$94	\$1,877	Dominated
Gum	11.913	\$12,870	0.0377	\$150	\$3,969	Dominated
Patch	11.921	\$12,935	0.0455	\$215	\$4,724	Dominated
Lozenge	11.935	\$12,965	0.0601	\$244	\$4,070	Dominated
Inhaler	11.964	\$13,226	0.0891	\$506	\$5,677	Dominated

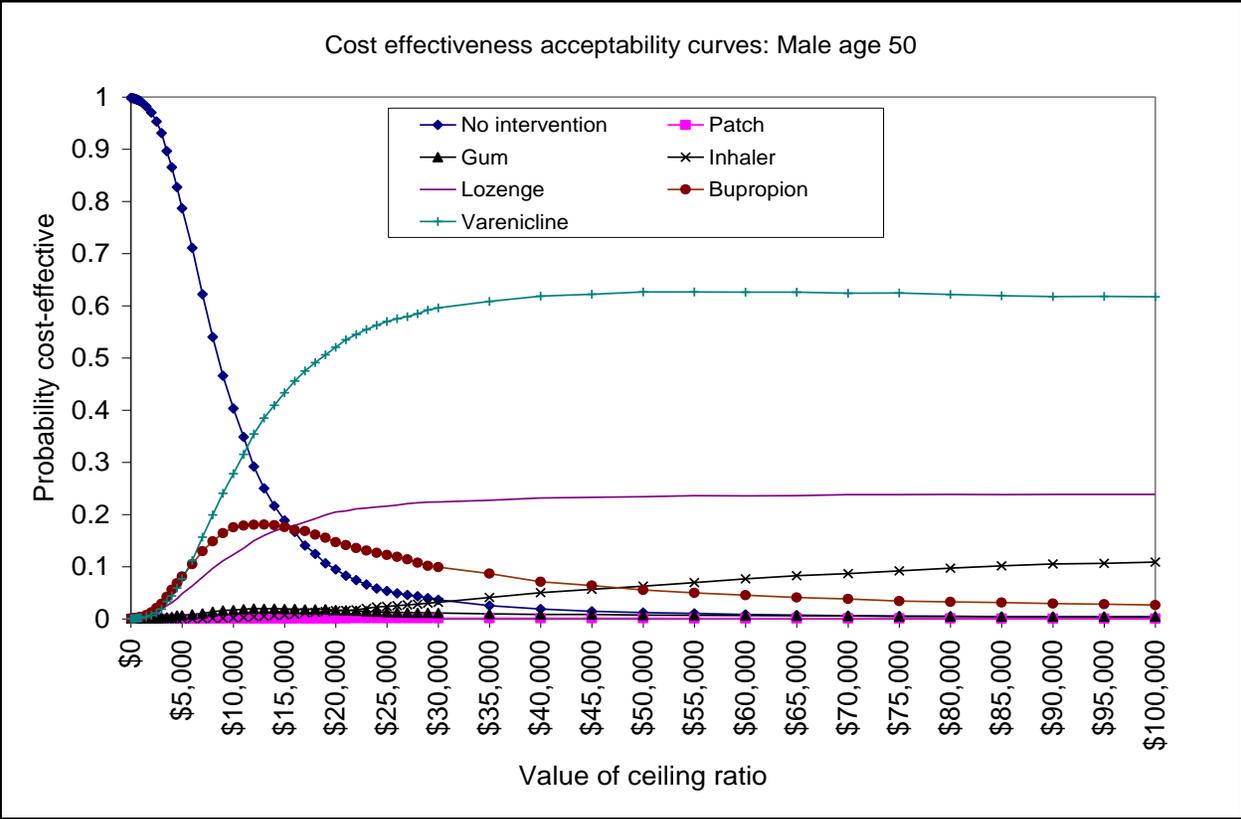
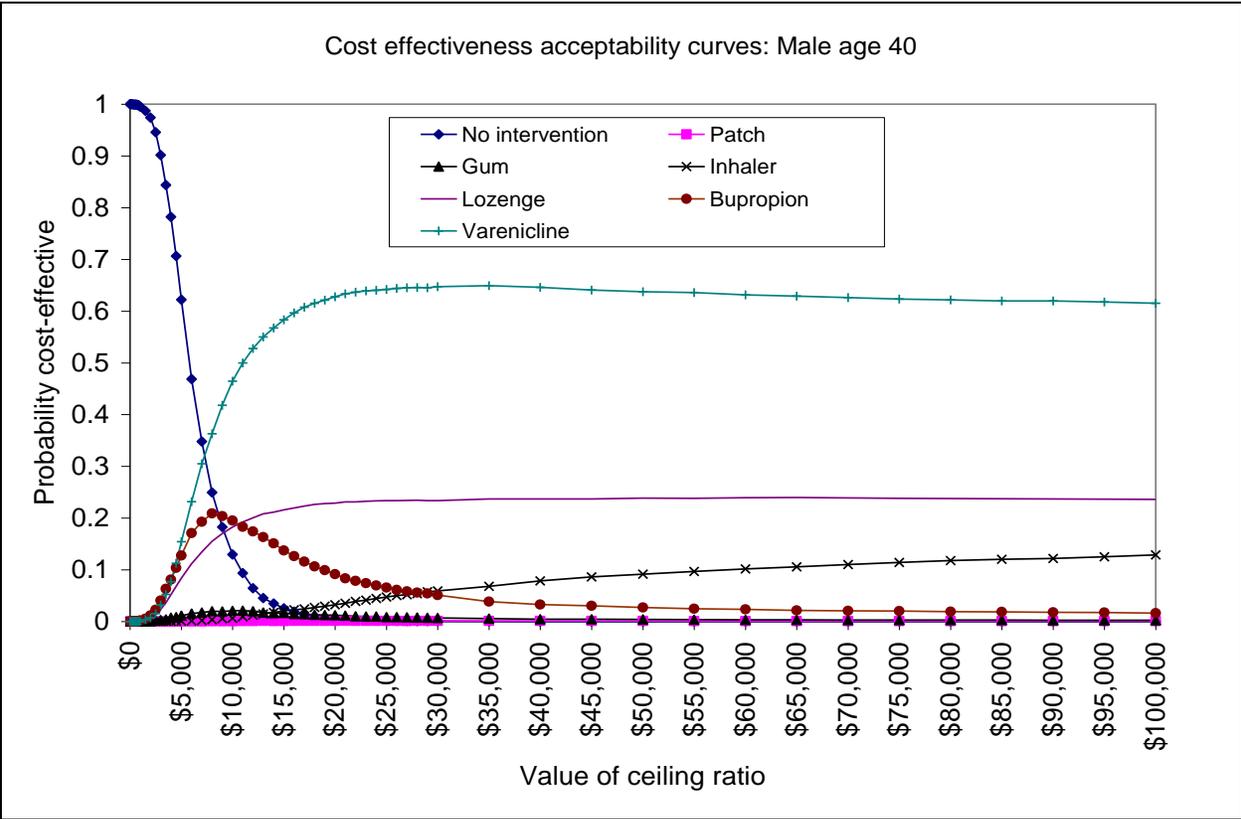
**Table A39: Sensitivity analyses of using CAR at 6 months as the definition of quit rate [Cost and QALYs]**

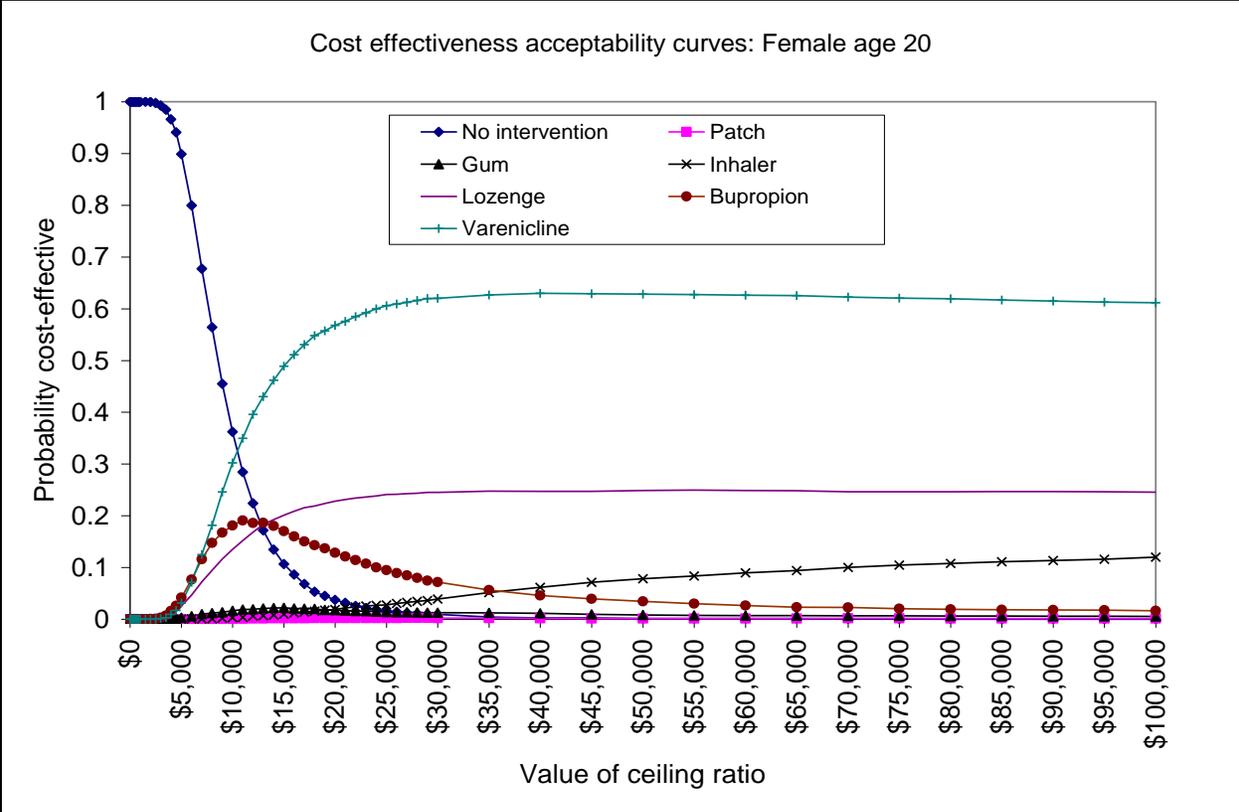
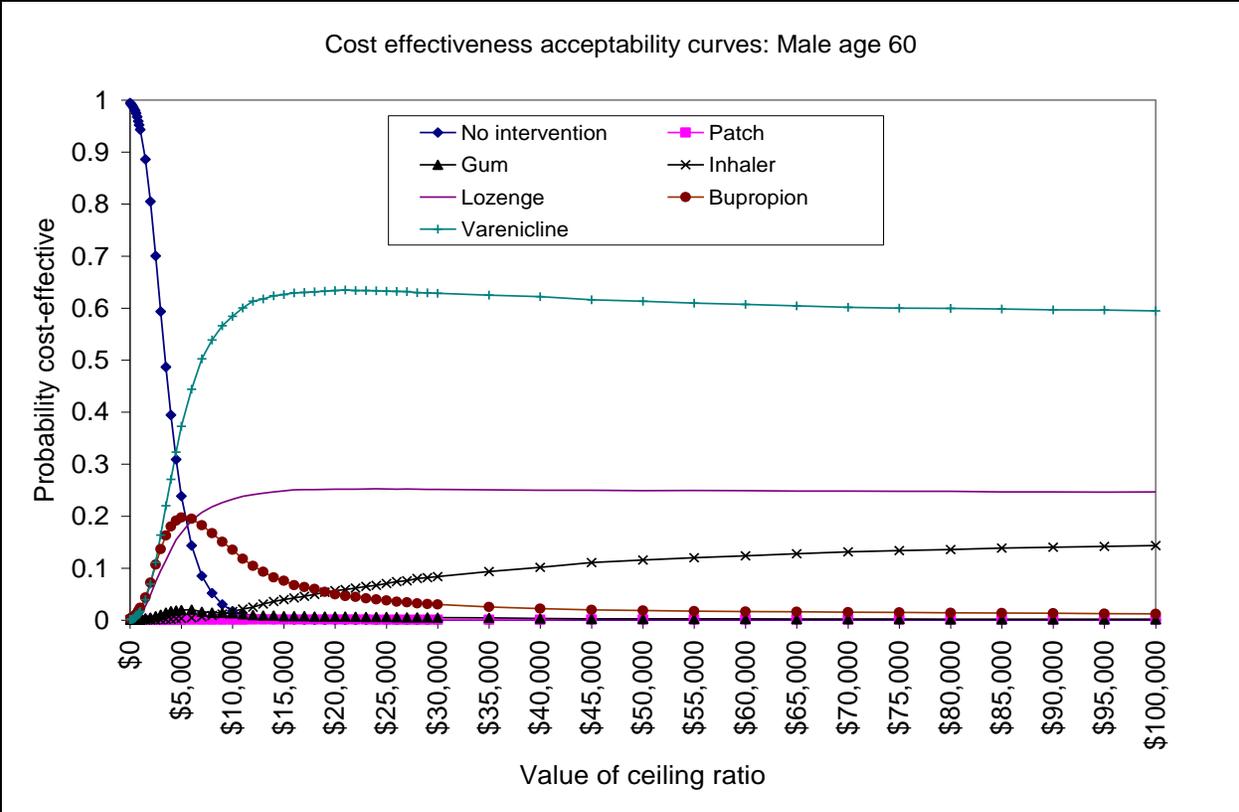
Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male aged 20 years</b>						
No intervention	14.3699	\$5,399	---	---	---	---
Gum	14.4016	\$5,597	0.0316	\$198	\$6,277	\$6,277
Varenicline	14.4116	\$5,717	0.0417	\$318	\$7,637	\$11,908
<b>Dominated therapies</b>						
Bupropion	14.3961	\$5,571	0.0262	\$172	\$6,586	Dominated
Patch	14.4003	\$5,679	0.0303	\$280	\$9,246	Dominated
Lozenge	14.4010	\$5,738	0.0310	\$339	\$10,937	Dominated
Inhaler	14.3997	\$6,059	0.0298	\$661	\$22,175	Dominated
<b>Male aged 40 years</b>						
No intervention	11.5470	\$12,062	---	---	---	---
Gum	11.5837	\$12,204	0.0367	\$143	\$3,882	\$3,882
Varenicline	11.5954	\$12,306	0.0484	\$245	\$5,052	\$8,728
<b>Dominated therapies</b>						
Bupropion	11.5774	\$12,188	0.0304	\$126	\$4,147	Dominated
Patch	11.5822	\$12,288	0.0352	\$227	\$6,437	Dominated
Lozenge	11.5830	\$12,346	0.0360	\$284	\$7,892	Dominated
Inhaler	11.5816	\$12,670	0.0346	\$608	\$17,565	Dominated
<b>Female aged 20 years</b>						
No intervention	14.6510	\$5,727	---	---	---	---
Gum	14.6803	\$5,923	0.0293	\$196	\$6,677	\$6,677
Varenicline	14.6897	\$6,042	0.0387	\$315	\$8,142	\$12,743
<b>Dominated therapies</b>						
Bupropion	14.6753	\$5,897	0.0243	\$170	\$7,009	Dominated
Patch	14.6791	\$6,005	0.0281	\$278	\$9,875	Dominated
Lozenge	14.6798	\$6,064	0.0288	\$337	\$11,697	Dominated
Inhaler	14.6787	\$6,385	0.0277	\$658	\$23,805	Dominated
<b>Female aged 40 years</b>						
No intervention	11.8499	\$12,772	---	---	---	---
Gum	11.8931	\$12,911	0.0433	\$139	\$3,202	\$3,202
Varenicline	11.9069	\$13,012	0.0570	\$239	\$4,196	\$7,316
<b>Dominated therapies</b>						
Bupropion	11.8857	\$12,895	0.0358	\$123	\$3,428	Dominated
Patch	11.8914	\$12,995	0.0415	\$223	\$5,372	Dominated
Lozenge	11.8923	\$13,053	0.0424	\$280	\$6,607	Dominated
Inhaler	11.8906	\$13,376	0.0408	\$604	\$14,818	Dominated

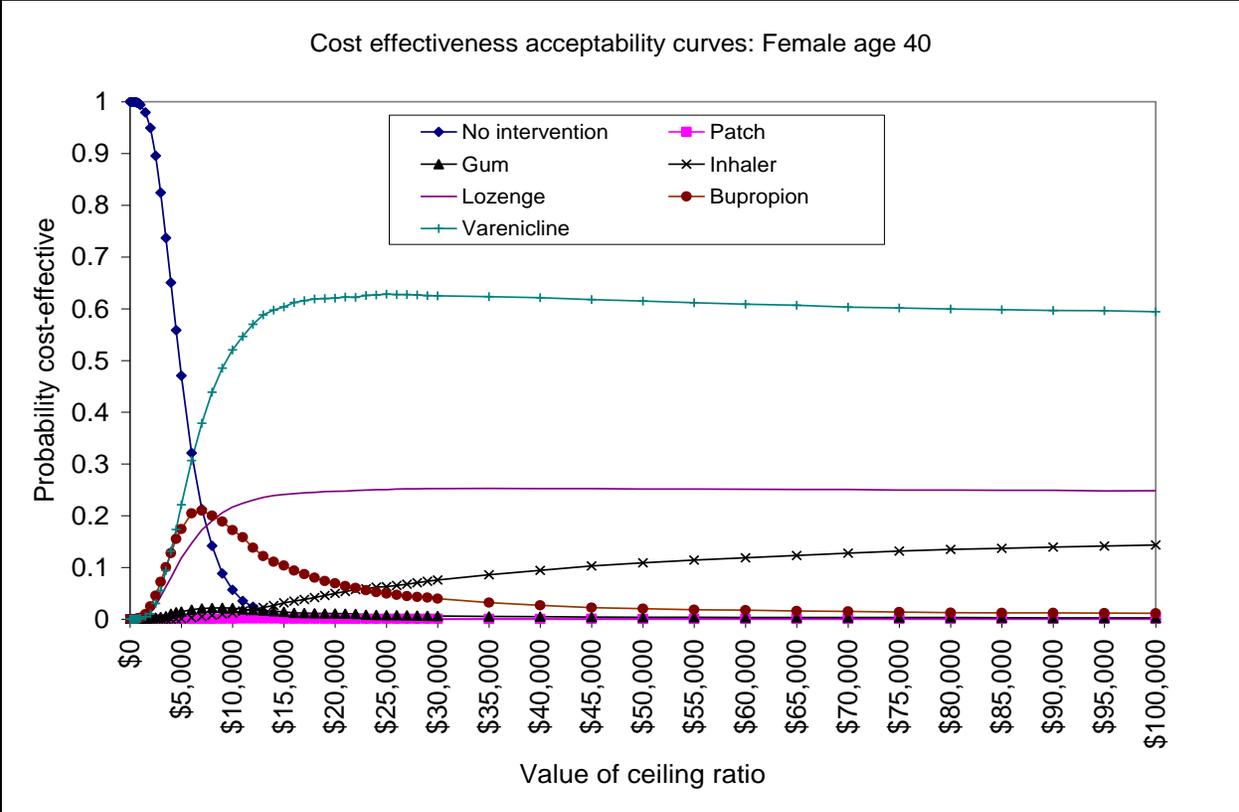
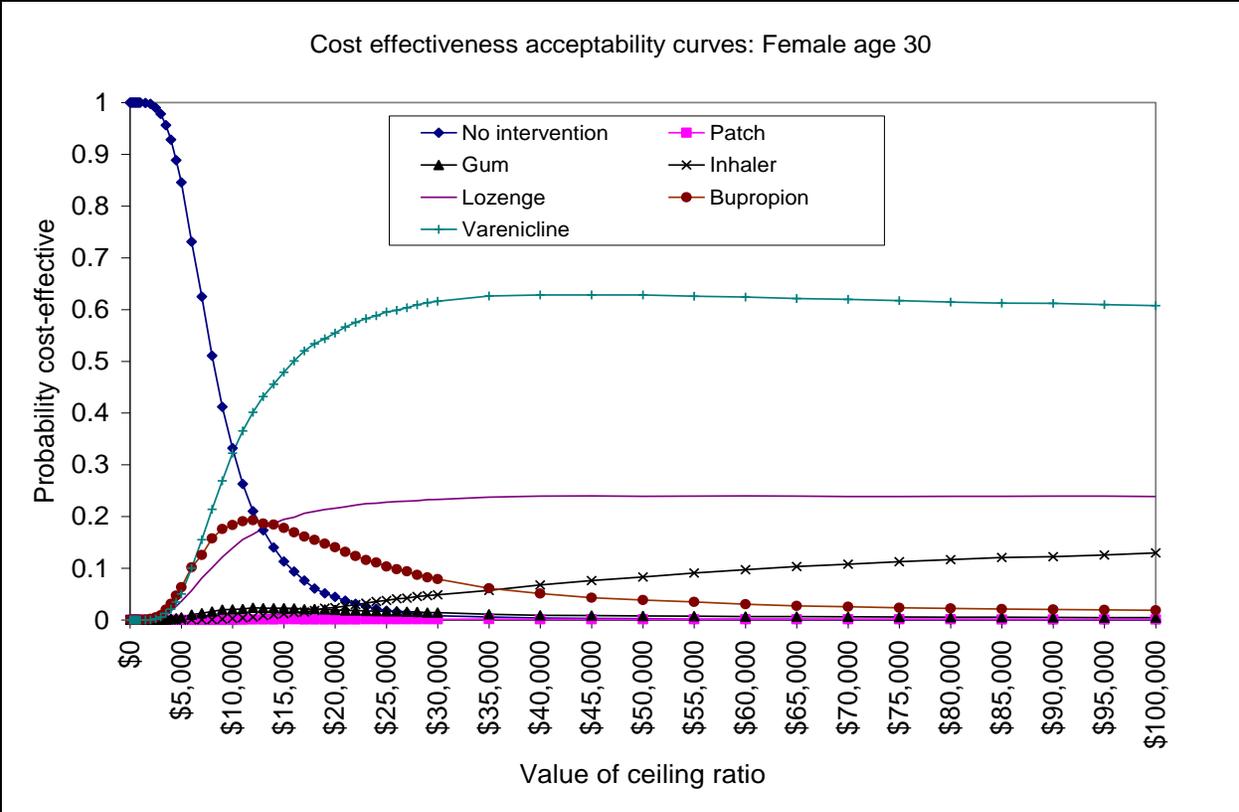
# APPENDIX 23: MCS RESULTS FOR GENERAL POPULATION

## CEAC by age at intervention and sex

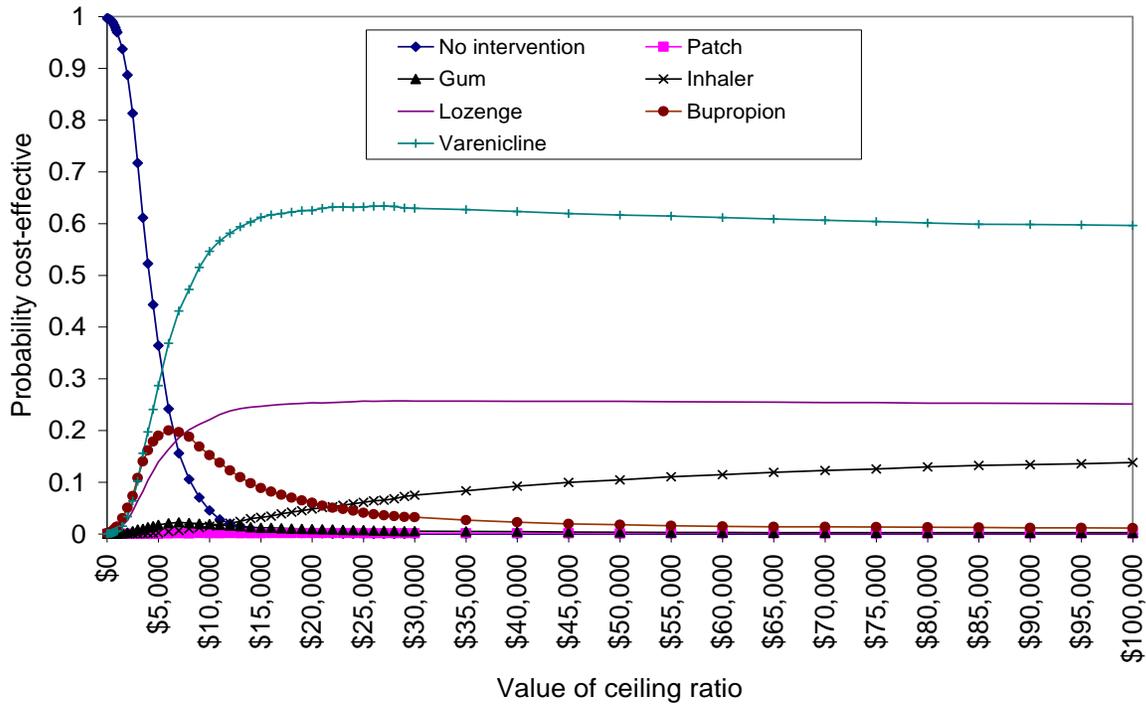




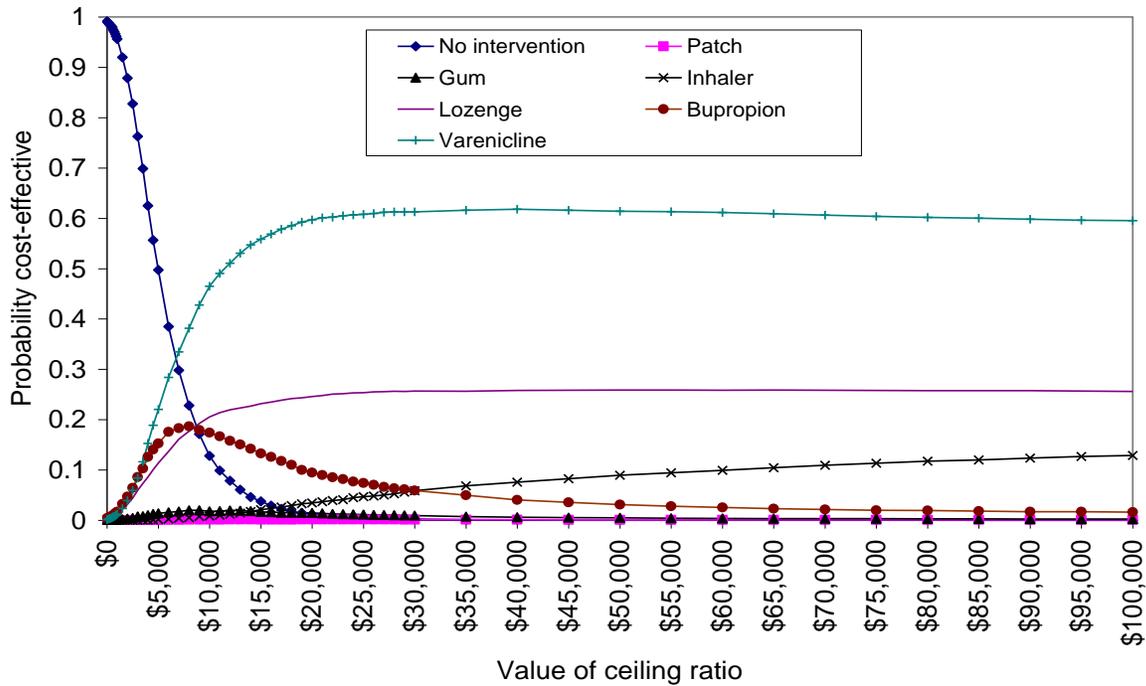




Cost effectiveness acceptability curves: Female age 50



Cost effectiveness acceptability curves: Female age 60



## APPENDIX 24: CALCULATION OF SMOKERS WHO ATTEMPT TO QUIT SMOKING

To determine the weights, we used the summary data from 2007 CTUMS.<sup>272</sup> In the CTUMS report, the number of smokers who attempted to quit smoking was reported by sex, four age groups (15-19, 20-24, 25-44 and 45+) and the number of quit attempts (no attempt, 1 attempt, 2 to 3 attempts, and 4 or more attempts).

Based on the information reported, the following is the number of current smokers who made at least one quit attempt.

	<b>Age group (years)</b>	<b>Number of current smokers who made at least 1 quit attempt</b>
Male	20-24	130,592
	25-44	423,120
	45+	388,168
Female	20-24	96,264
	25-44	396,552
	45+	332,332

Source: CTUMS<sup>272</sup>

The CTUMS summary report only reported the number of quit attempts by age group, not by each age. Therefore, we applied 2007 Canadian population estimates by age (one-year increments) and sex<sup>507</sup> to estimate the number of quit attempts at the ages of 20, 30, 40, 50, and 60 years. More specifically, we first calculated age distribution within each age group (20-24, 25-44 and 45+). For example, the age distribution of males between 20 and 24 years old were calculated as 19.4% (20 years old), 19.9% (21 years old), 20.2% (22 years old), 20.3% (23 years old) and 20.2% (24 years old) (see table below). This means that, in 2007, males aged 20 years represented 19.4% of the total male population aged between 20 and 24 years. These proportions were applied to the number of current smokers who made at least one quit attempt for males aged between 20 and 24 years, assuming that the age distribution of the number of smokers who attempt to quit smoking was comparable to the population age distribution of the same age group. Therefore, the estimated number of 20-year-old male smokers who attempted to quit smoking was 25,277 (= 130,592\*0.193557; the difference was due to rounding of proportions). The population of females and other ages were calculated in the same manner.

**Table A41: Age distribution within age group**

<b>Age group 20-24</b>							
<b>Age</b>	<b>20</b>	<b>21</b>	<b>22</b>	<b>23</b>	<b>24</b>	<b>Total (age 20-24)</b>	
Male	<b>19.3557%</b>	19.8960%	20.2185%	20.2803%	20.2495%	100.0%	
Female	<b>19.4201%</b>	19.9198%	20.1223%	20.2713%	20.2665%	100.0%	
<b>Age group 25-44</b>							
<b>Age</b>	<b>25</b>	<b>26</b>	<b>27</b>	<b>28</b>	<b>29</b>	<b>30</b>	<b>31</b>
Male	4.8652%	4.8644%	4.8386%	4.7336%	4.6780%	<b>4.7088%</b>	4.7433%
Female	4.7672%	4.8234%	4.8128%	4.7433%	4.6805%	<b>4.7309%</b>	4.7264%
<i>Age group 25-44 continued</i>							
<b>Age</b>	<b>32</b>	<b>33</b>	<b>34</b>	<b>35</b>	<b>36</b>	<b>37</b>	<b>38</b>
Male	4.7571%	4.6531%	4.7219%	4.8270%	5.0040%	5.0184%	4.9569%
Female	4.7375%	4.6629%	4.7095%	4.8036%	5.0030%	5.0097%	4.9828%
<i>Age group 25-44 continued</i>							
<b>Age</b>	<b>39</b>	<b>40</b>	<b>41</b>	<b>42</b>	<b>43</b>	<b>44</b>	<b>Total (age 25-44)</b>
Male	4.9363%	<b>4.9972%</b>	5.2796%	5.6512%	5.8503%	5.9152%	100%
Female	4.9769%	<b>5.0380%</b>	5.3084%	5.6846%	5.8735%	5.9253%	100%
<b>Age group 45+</b>							
<b>Age</b>	<b>45</b>	<b>46</b>	<b>47</b>	<b>48</b>	<b>49</b>	<b>50</b>	<b>51</b>
Male	4.3320%	4.3481%	4.2847%	4.1632%	4.1330%	<b>4.0251%</b>	3.8888%
Female	3.9126%	3.9515%	3.9023%	3.8157%	3.7666%	<b>3.7010%</b>	3.5871%
<i>Age group 45+ continued</i>							
<b>Age</b>	<b>52</b>	<b>53</b>	<b>54</b>	<b>55</b>	<b>56</b>	<b>57</b>	<b>58</b>
Male	3.8422%	3.6882%	3.5159%	3.3949%	3.3245%	3.2453%	3.1743%
Female	3.5646%	3.4437%	3.2890%	3.1681%	3.1084%	3.0327%	2.9774%
<i>Age group 45+ continued</i>							
<b>Age</b>	<b>59</b>	<b>60</b>	<b>61</b>	<b>62</b>	<b>63</b>	<b>64</b>	<b>65</b>
Male	3.1700%	<b>3.1426%</b>	2.6916%	2.5010%	2.4183%	2.3325%	2.1499%
Female	2.9665%	<b>2.9455%</b>	2.5313%	2.3521%	2.2924%	2.2109%	2.0637%
<i>Age group 45+ continued</i>							
<b>Age</b>	<b>66</b>	<b>67</b>	<b>68</b>	<b>69</b>	<b>70</b>	<b>71</b>	<b>72</b>
Male	2.0331%	1.8946%	1.8206%	1.7336%	1.6407%	1.6142%	1.5359%
Female	1.9829%	1.8598%	1.7962%	1.7220%	1.6506%	1.6402%	1.5854%
<i>Age group 45+ continued</i>							
<b>Age</b>	<b>73</b>	<b>74</b>	<b>75</b>	<b>76</b>	<b>77</b>	<b>78</b>	<b>79</b>
Male	1.4705%	1.4542%	1.4116%	1.3488%	1.2608%	1.1472%	1.0794%
Female	1.5253%	1.5328%	1.5107%	1.4870%	1.4313%	1.3482%	1.3054%
<i>Age group 45+ continued</i>							
<b>Age</b>	<b>80</b>	<b>81</b>	<b>82</b>	<b>83</b>	<b>84</b>	<b>85</b>	<b>86</b>
Male	0.9766%	0.8997%	0.8093%	0.7158%	0.6368%	0.5631%	0.4809%
Female	1.2418%	1.1995%	1.1299%	1.0635%	0.9790%	0.9141%	0.8164%
<i>Age group 45+ continued</i>							
<b>Age</b>	<b>87</b>	<b>88</b>	<b>89</b>	<b>90+</b>	<b>Total (age 45+)</b>		
Male	0.3913%	0.2958%	0.2365%	0.7826%	100%		
Female	0.7083%	0.5663%	0.4749%	1.9455%	100%		

Source: Statistics Canada, Demographic estimates compendium 2007<sup>507</sup>

Using the data above, Table A52 shows the estimated number of smokers who made at least one quit attempt by age and sex is shown below.

<b>Table A42: Estimated number of smokers who attempt to quit by age and sex</b>		
<b>Age</b>	<b>Male</b>	<b>Female</b>
20	25,277	18,695
30	19,924	18,761
40	21,144	19,978
50	15,624	12,300
60	12,199	9,789
Total	173,691	

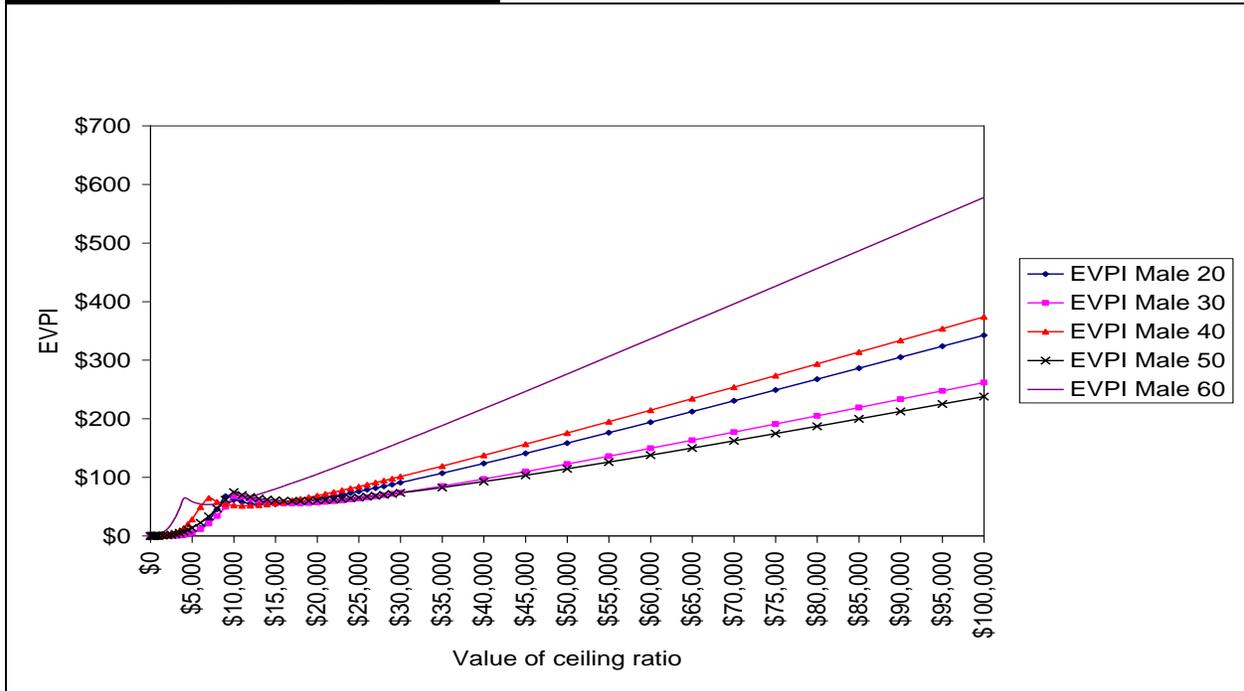
Based on the above, weights were calculated by dividing the number of smokers who attempt to quit for each age and sex by total number of smokers who attempt to quit smoking. Table A53 shows the weights:

<b>Table A43: Estimated % of smokers who attempt to quit for each age and sex over total smokers who attempt to quit smoking</b>		
<b>Age</b>	<b>Male</b>	<b>Female</b>
20	0.15	0.11
30	0.11	0.11
40	0.12	0.12
50	0.09	0.07
60	0.07	0.06
Total	1.00*	

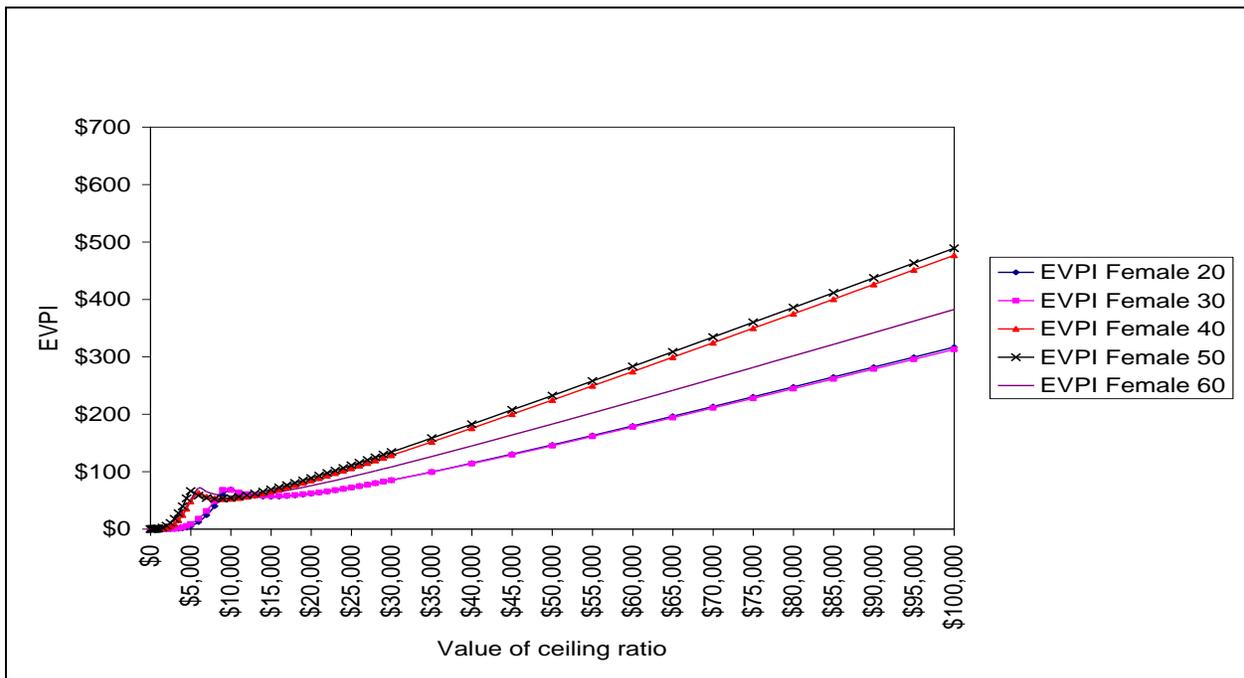
\*Total may not add to 100% due to rounding

# APPENDIX 25: EVPI BY AGE AND GENDER FOR GENERAL POPULATION

## EVPI for males (general population)



## EVPI for females (general population)



## APPENDIX 26: SENSITIVITY ANALYSES FOR MODELS FOR COST-EFFECTIVENESS OF ADDING BEHAVIOURAL INTERVENTION

<b>Table A44: Sensitivity analysis of patient co-payment of 30% on patch</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. patch)</b>	<b>Incremental cost (vs. patch)</b>	<b>ICER</b>
<b>Male</b>					
Patch	11.603	\$12,062	---	---	---
Patch+Behaviour	11.600	\$12,087	-0.003	\$25	Dominated
<b>Female</b>					
Patch	11.917	\$12,766	---	---	---
Patch+Behaviour	11.913	\$12,791	-0.004	\$25	Dominated

<b>Table A45: Sensitivity analysis of low patch price</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. patch)</b>	<b>Incremental cost (vs. patch)</b>	<b>ICER</b>
<b>Male</b>					
Patch	11.603	\$12,069	---	---	---
Patch+Behaviour	11.600	\$12,094	-0.003	\$25	Dominated
<b>Female</b>					
Patch	11.917	\$12,773	---	---	---
Patch+Behaviour	11.913	\$12,798	-0.004	\$25	Dominated

<b>Table A46: Sensitivity analysis of 3% discount rate</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. patch)</b>	<b>Incremental cost (vs. patch)</b>	<b>ICER</b>
<b>Male</b>					
Patch	14.796	\$18,072	---	---	---
Patch+Behaviour	14.791	\$18,099	-0.005	\$27	Dominated
<b>Female</b>					
Patch	15.389	\$19,464	---	---	---
Patch+Behaviour	15.383	\$19,491	-0.006	\$27	Dominated

<b>Table A47: Sensitivity analysis of 0% discount rate</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. patch)</b>	<b>Incremental cost (vs. patch)</b>	<b>ICER</b>
<b>Male</b>					
Patch	22.887	\$36,070	---	---	---
Patch+Behaviour	22.876	\$36,097	-0.010	\$27	Dominated
<b>Female</b>					
Patch	24.561	\$40,398	---	---	---
Patch+Behaviour	24.549	\$40,425	-0.012	\$27	Dominated

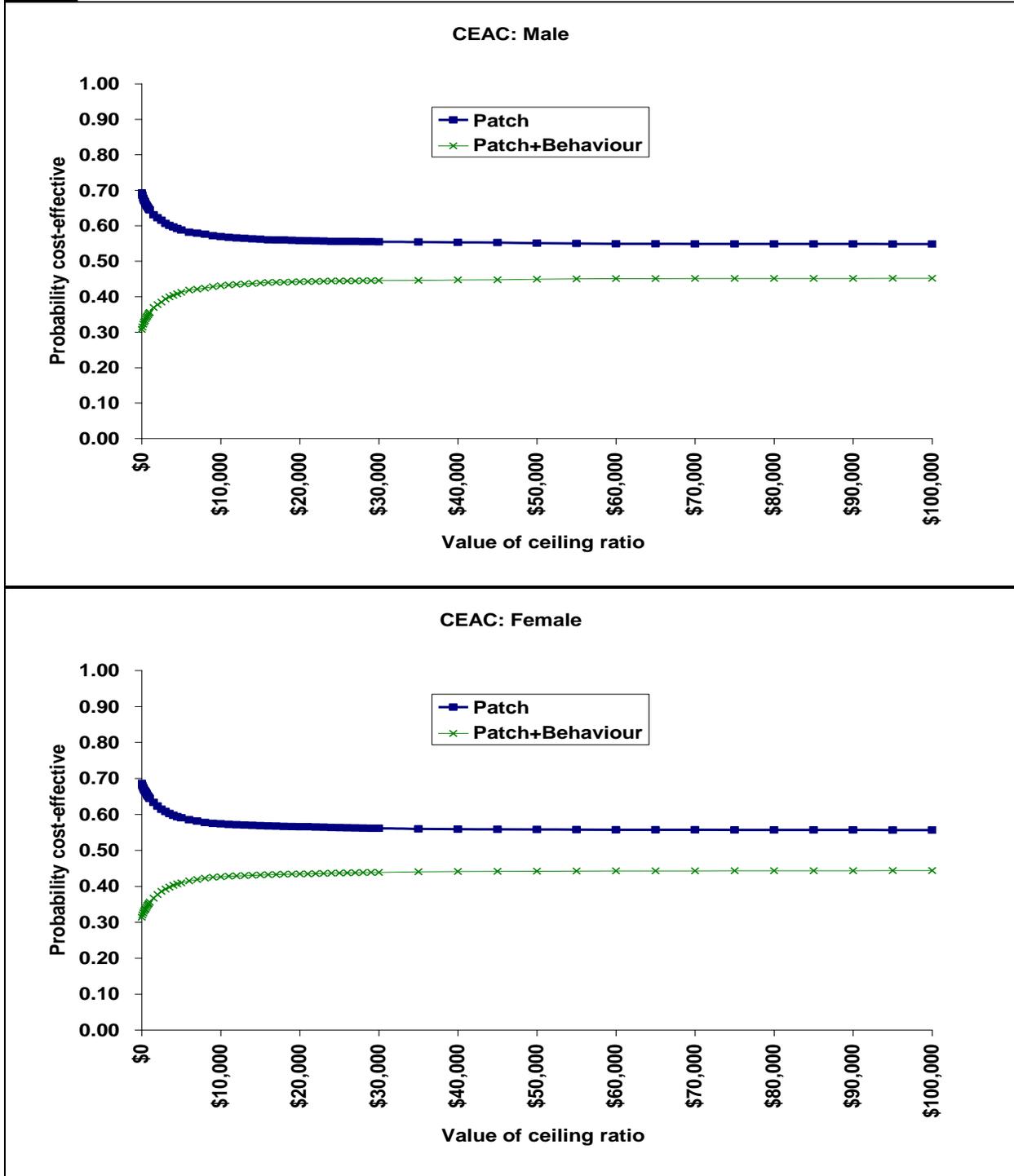
<b>Table A48: Sensitivity analysis of using counselling cost based on BC rate</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. patch)</b>	<b>Incremental cost (vs. patch)</b>	<b>ICER</b>
<b>Male</b>					
Patch	11.603	\$12,102	---	---	---
Patch+Behaviour	11.600	\$12,181	-0.003	\$79	Dominated
<b>Female</b>					
Patch	11.917	\$12,806	---	---	---
Patch+Behaviour	11.913	\$12,885	-0.004	\$79	Dominated

<b>Table A49: Sensitivity analysis of applying counselling time of 10 minutes instead of 15 minutes</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. patch)</b>	<b>Incremental cost (vs. patch)</b>	<b>ICER</b>
<b>Male</b>					
Patch	11.603	\$12,102	---	---	---
Patch+Behaviour	11.600	\$12,121	-0.003	\$19	Dominated
<b>Female</b>					
Patch	11.917	\$12,806	---	---	---
Patch+Behaviour	11.913	\$12,825	-0.004	\$19	Dominated

<b>Table A50: Sensitivity analysis of using CAR at 6 mo as a definition of quit rate</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. patch + behaviour)</b>	<b>Incremental cost (vs. patch + behaviour)</b>	<b>ICER</b>
<b>Male</b>					
Patch+Behaviour	11.646	\$11,834	---	---	---
Patch	11.630	\$12,055	-0.016	\$221	Dominated
<b>Female</b>					
Patch+Behaviour	11.966	\$12,534	---	---	---
Patch	11.948	\$12,757	-0.018	\$223	Dominated

# APPENDIX 27: MCS FOR MODELS FOR COST-EFFECTIVENESS OF ADDING BEHAVIOURAL INTERVENTION

## CEAC



## APPENDIX 28: SENSITIVITY ANALYSES FOR PAY OR COPAY MODELS

<b>Table A51: Sensitivity analysis of low patch price</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no Reimbursement)</b>	<b>Incremental cost (vs. no Reimbursement)</b>	<b>ICER</b>
<b>Male</b>					
No Reimbursement	0.494	\$447	---	---	---
Reimbursement	1.282	\$1,231	0.788	\$784	\$995
<b>Female</b>					
No Reimbursement	0.510	\$474	---	---	---
Reimbursement	1.321	\$1,303	0.811	\$829	\$1,022

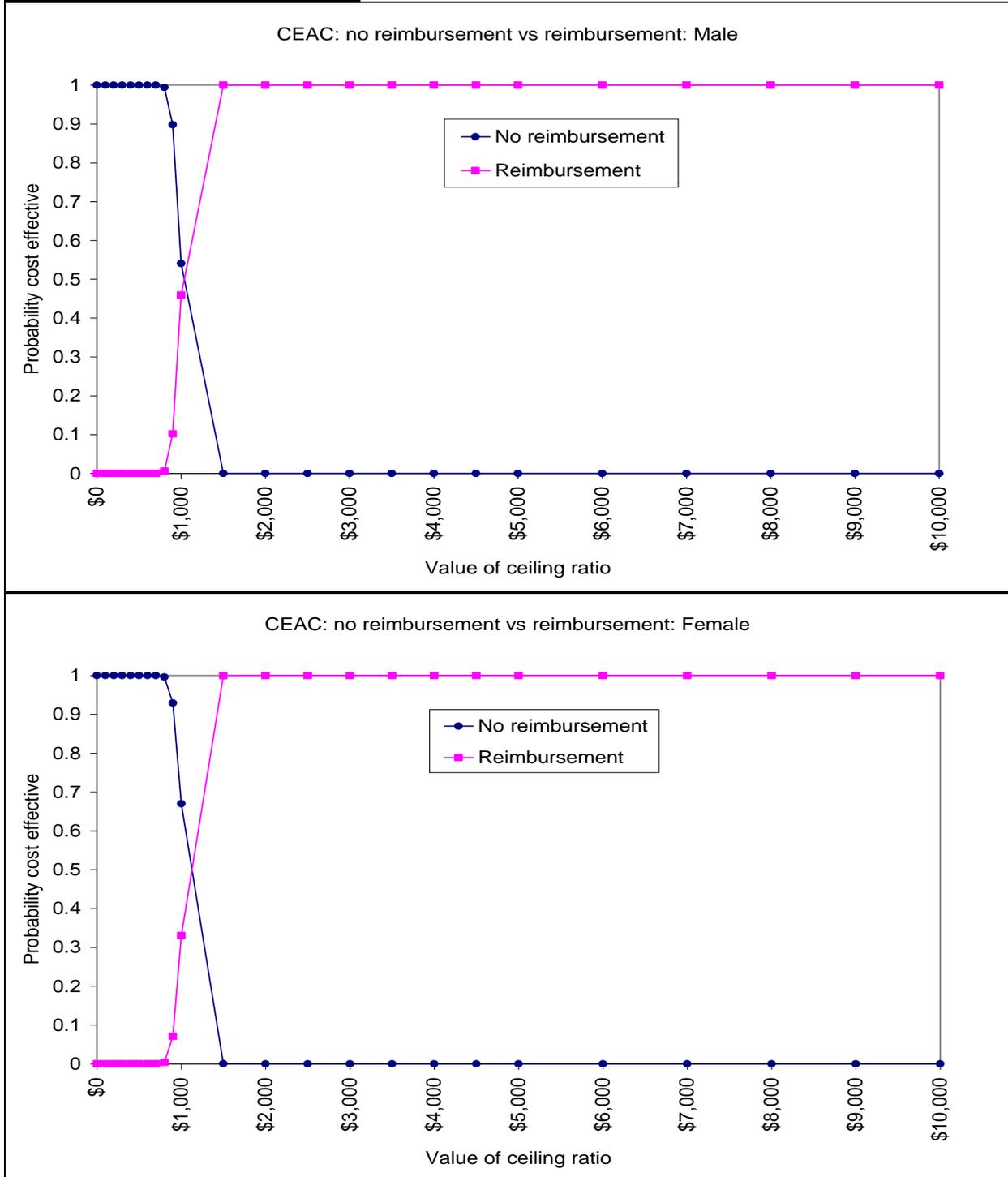
<b>Table A52: Sensitivity analysis of low gum dosage</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no Reimbursement)</b>	<b>Incremental cost (vs. no Reimbursement)</b>	<b>ICER</b>
<b>Male</b>					
No Reimbursement	0.494	\$447	---	---	---
Reimbursement	1.282	\$1,234	0.788	\$776	\$999
<b>Female</b>					
No Reimbursement	0.510	\$474	---	---	---
Reimbursement	1.321	\$1,306	0.811	\$832	\$1,026

<b>Table A53: Sensitivity analysis of 3% discount rate</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no Reimbursement)</b>	<b>Incremental cost (vs. no Reimbursement)</b>	<b>ICER</b>
<b>Male</b>					
No Reimbursement	0.635	\$685	---	---	---
Reimbursement	1.644	\$1,863	1.009	\$1,178	\$1,168
<b>Female</b>					
No Reimbursement	0.665	\$739	---	---	---
Reimbursement	1.717	\$2,008	1.052	\$1,268	\$1,206

<b>Table A54: Sensitivity analysis of 0% discount rate</b>					
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no Reimbursement)</b>	<b>Incremental cost (vs. no Reimbursement)</b>	<b>ICER</b>
<b>Male</b>					
No Reimbursement	1.002	\$1,424	---	---	---
Reimbursement	2.577	\$3,800	1.575	\$2,377	\$1,509
<b>Female</b>					
No Reimbursement	1.082	\$1,601	---	---	---
Reimbursement	2.778	\$4,265	1.696	\$2,665	\$1,571

# APPENDIX 29: MCS RESULTS FOR PAY OR COPAY MODEL

## CEAC for pay or co-pay model\*



\*For ease of presentation, results for values of ceiling ratio between \$10,000 and \$100,000 were suppressed. However, results for values greater than \$10,000 were consistent with these at \$10,000.

## APPENDIX 30: SENSITIVITY ANALYSES OF MODELS FOR PATIENTS WITH CARDIOVASCULAR OR SMOKING-RELATED DISEASES

<b>Table A55: Sensitivity analysis of low patch price</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male</b>						
No intervention	4.744	\$27,363	---	---	---	---
Bupropion	4.792	\$27,522	0.048	\$159	\$3,312	\$3,312
<b>Dominated therapies</b>						
NRT	4.789	\$27,862	0.044	\$498	\$11,244	Dominated
<b>Female</b>						
No intervention	5.354	\$28,418	---	---	---	---
Bupropion	5.389	\$28,551	0.035	\$133	\$3,759	\$3,759
<b>Dominated therapies</b>						
NRT	5.386	\$28,892	0.033	\$475	\$14,493	Dominated

<b>Table A56: Sensitivity analysis of 9-month treatment of patch and inhaler instead of 3 month</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male</b>						
No intervention	4.744	\$27,363	---	---	---	---
Bupropion	4.792	\$27,522	0.048	\$159	\$3,312	\$3,312
<b>Dominated therapies</b>						
NRT	4.789	\$28,816	0.044	\$1,452	\$32,780	Dominated
<b>Female</b>						
No intervention	5.354	\$28,418	---	---	---	---
Bupropion	5.389	\$28,551	0.035	\$133	\$3,759	\$3,759
<b>Dominated therapies</b>						
NRT	5.386	\$29,847	0.033	\$1,429	\$43,635	Dominated

**Table A57: Sensitivity analysis of co-payment of 30%**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male</b>						
No intervention	4.744	\$27,363	---	---	---	---
Bupropion	4.792	\$27,491	0.048	\$127	\$2,654	\$2,654
<b>Dominated therapies</b>						
NRT	4.789	\$27,818	0.044	\$455	\$10,270	Dominated
<b>Female</b>						
No intervention	5.354	\$28,418	---	---	---	---
Bupropion	5.389	\$28,519	0.035	\$102	\$2,869	\$2,869
<b>Dominated therapies</b>						
NRT	5.386	\$28,849	0.033	\$432	\$13,174	Dominated

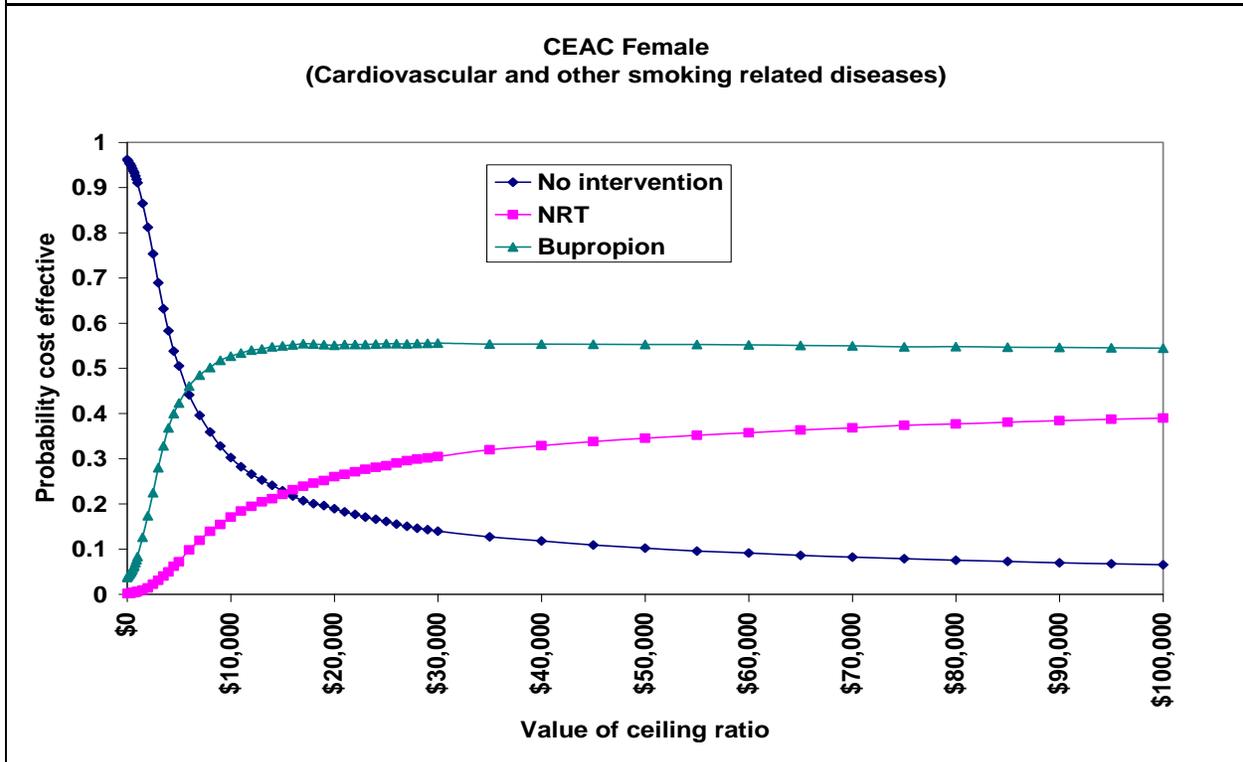
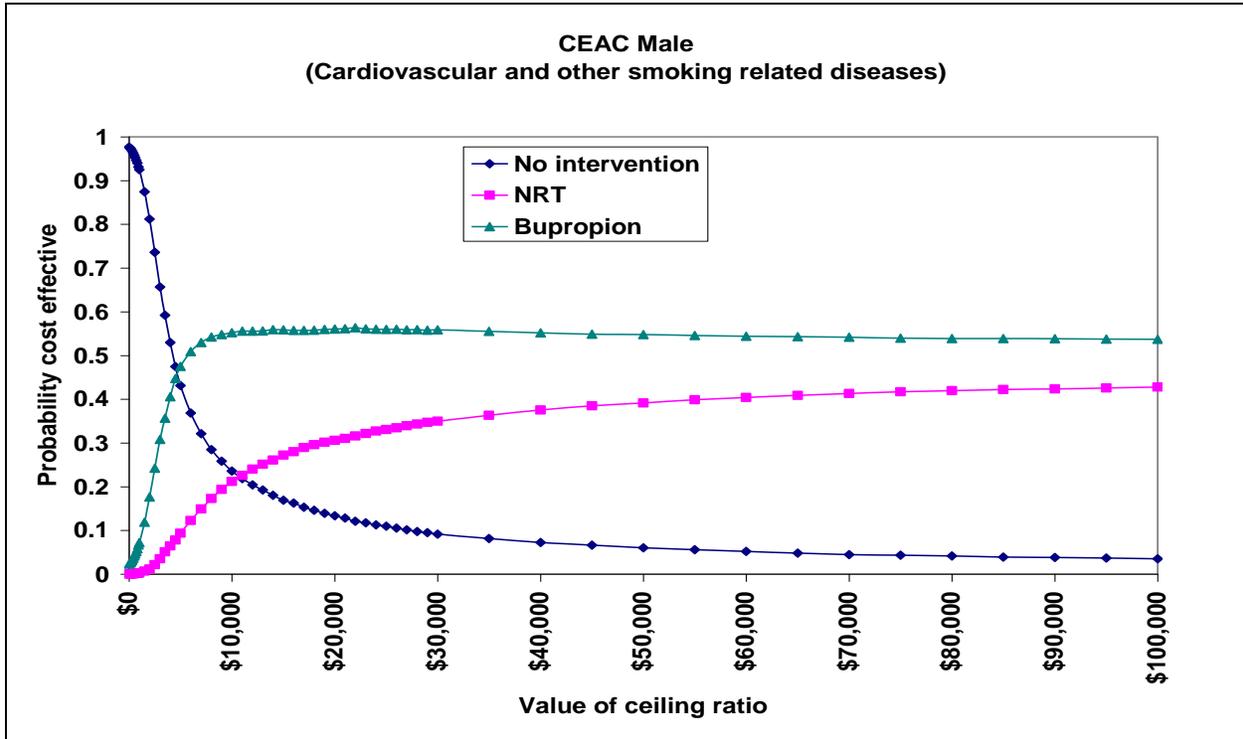
**Table A58: Sensitivity analysis of 3% discount rate**

Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male</b>						
No intervention	5.484	\$32,086	---	---	---	---
Bupropion	5.549	\$32,307	0.065	\$221	\$3,401	\$3,401
<b>Dominated therapies</b>						
NRT	5.544	\$32,689	0.060	\$603	\$10,056	Dominated
<b>Female</b>						
No intervention	6.305	\$33,844	---	---	---	---
Bupropion	6.355	\$34,024	0.051	\$181	\$3,580	\$3,580
<b>Dominated therapies</b>						
NRT	6.351	\$34,410	0.047	\$566	\$12,129	Dominated

<b>Table A59: Sensitivity analysis of discount rate of 0%</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male</b>						
No intervention	6.995	\$41,968	---	---	---	---
Bupropion	7.101	\$42,358	0.107	\$390	\$3,663	\$3,663
<b>Dominated therapies</b>						
NRT	7.093	\$42,751	0.098	\$784	\$7,965	Dominated
<b>Female</b>						
No intervention	8.351	\$45,689	---	---	---	---
Bupropion	8.442	\$46,010	0.091	\$322	\$3,546	\$3,546
<b>Dominated therapies</b>						
NRT	8.435	\$46,409	0.084	\$720	\$8,600	Dominated

<b>Table A60: Sensitivity analysis of CAR at 6 months as the definition of quit rate</b>						
<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male</b>						
No intervention	4.800	\$27,437	---	---	---	---
Bupropion	4.868	\$27,645	0.068	\$209	\$3,062	\$3,062
<b>Dominated therapies</b>						
NRT	4.824	\$28,002	0.024	\$565	\$23,498	Dominated
<b>Female</b>						
No intervention	5.395	\$28,461	---	---	---	---
Bupropion	5.445	\$28,632	0.050	\$171	\$3,398	\$3,398
<b>Dominated therapies</b>						
NRT	5.412	\$29,012	0.018	\$552	\$31,071	Dominated

# APPENDIX 31: MCS RESULTS FOR MODELS FOR PATIENTS WITH CARDIOVASCULAR OR OTHER SMOKING RELATED DISEASES



## APPENDIX 32: SENSITIVITY ANALYSES OF MODELS FOR HOSPITALIZED PATIENTS

Table A61: Sensitivity analysis of low patch price						
Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male</b>						
No intervention	4.616	\$28,000	---	---	---	---
Bupropion	4.643	\$28,206	0.027	\$207	\$7,658	\$7,658
Patch	4.645	\$28,298	0.029	\$298	\$10,352	\$50,372
<b>Female</b>						
No intervention	5.245	\$28,893	---	---	---	---
Bupropion	5.264	\$29,086	0.019	\$193	\$10,143	\$10,143
Patch	5.266	\$29,177	0.020	\$284	\$13,958	\$70,640

Table A62: Sensitivity analysis of including 30% patient co-payment						
Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male</b>						
No intervention	4.616	\$28,000	---	---	---	---
Bupropion	4.643	\$28,153	0.027	\$153	\$5,683	\$5,683
Patch	4.645	\$28,295	0.029	\$295	\$10,261	\$78,282
<b>Female</b>						
No intervention	5.245	\$28,893	---	---	---	---
Bupropion	5.264	\$29,033	0.019	\$140	\$7,345	\$7,345
Patch	5.266	\$29,174	0.020	\$281	\$13,829	\$110,169

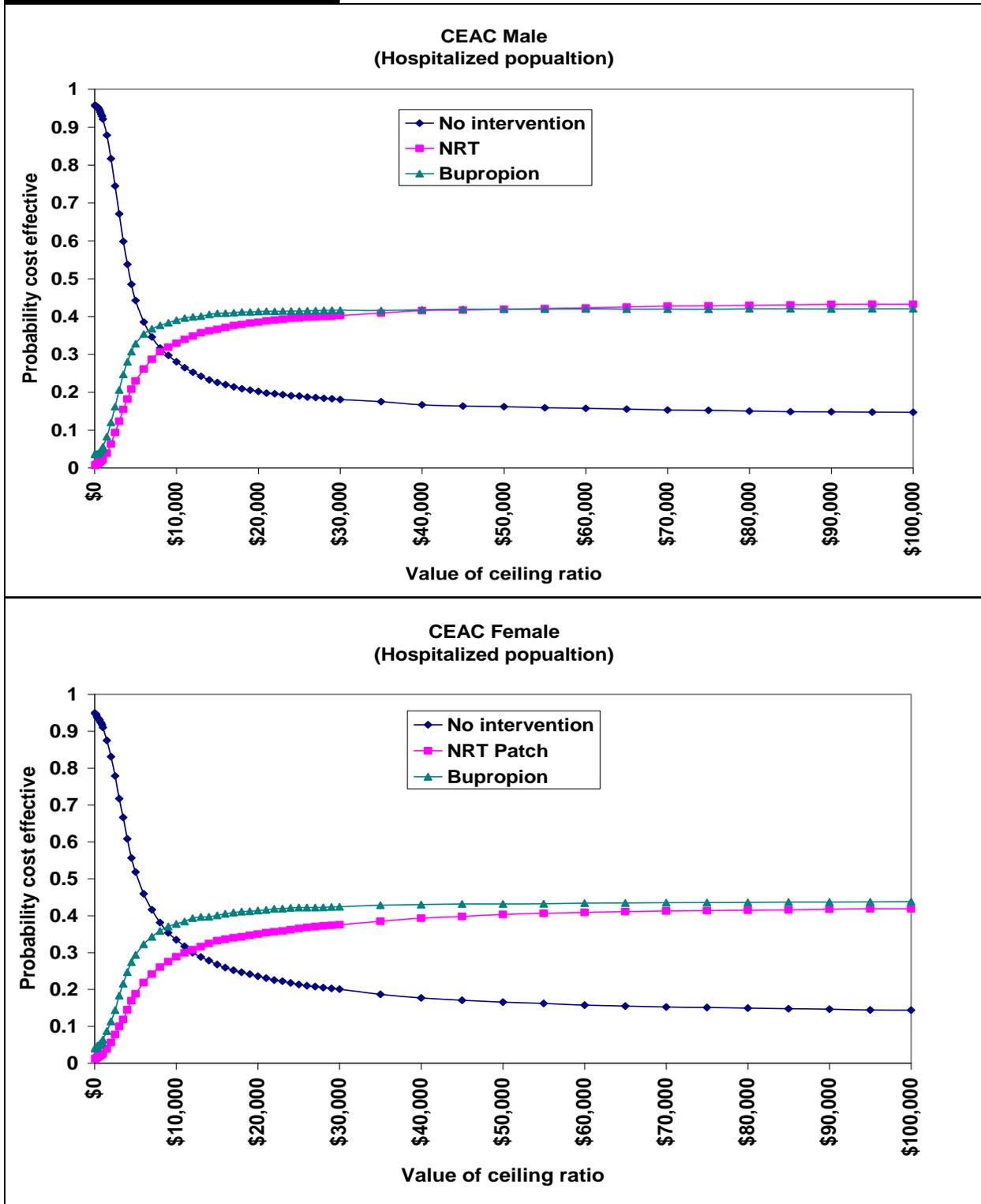
Table A63: Sensitivity analysis of using 3% discount rate						
Intervention	QALYs	Cost	Incremental QALYs (vs. no intervention)	Incremental cost (vs. no intervention)	ICER (vs. no intervention)	ICER (sequential)
<b>Male</b>						
No intervention	5.315	\$32,617	---	---	---	---
Bupropion	5.351	\$32,861	0.036	\$244	\$6,799	\$6,799
Patch	5.354	\$33,026	0.038	\$409	\$10,680	\$68,334
<b>Female</b>						
No intervention	6.156	\$34,191	---	---	---	---
Bupropion	6.183	\$34,413	0.027	\$222	\$8,331	\$8,331
Patch	6.185	\$34,576	0.028	\$386	\$13,549	\$91,086

**Table A64: Sensitivity analysis of using 0% discount rate**

<b>Intervention</b>	<b>QALYs</b>	<b>Cost</b>	<b>Incremental QALYs (vs. no intervention)</b>	<b>Incremental cost (vs. no intervention)</b>	<b>ICER (vs. no intervention)</b>	<b>ICER (sequential)</b>
<b>Male</b>						
No intervention	6.736	\$42,175	---	---	---	---
Bupropion	6.794	\$42,514	0.057	\$339	\$5,914	\$5,914
Patch	6.798	\$42,695	0.061	\$520	\$8,489	\$46,740
<b>Female</b>						
No intervention	8.106	\$45,640	---	---	---	---
Bupropion	8.152	\$45,940	0.047	\$300	\$6,431	\$6,431
Patch	8.156	\$46,118	0.050	\$478	\$9,594	\$56,588

# APPENDIX 33: MCS RESULTS FOR HOSPITALIZED PATIENTS

## CEAC for hospitalized patients



## APPENDIX 34: SMOKING PREVALENCE BY PROVINCES IN 2007 (AGE 15+)

Province	Number of current smokers*	Percentage of total population (age 15+)
Newfoundland and Labrador	90,100	21.2%
Prince Edward Island	20,976	18.4%
Nova Scotia	158,916	20.4%
New Brunswick	132,076	21.2%
Quebec	1,380,988	21.7%
Ontario	1,899,352	18.2%
Manitoba	187,657	19.9%
Saskatchewan	189,600	24.0%
Alberta	582,274	20.9%
British Columbia	524,592	14.4%

Source: CTUMS 2007 (with further calculations)<sup>5</sup>

\*Defined as current daily or occasional cigarette smokers

## APPENDIX 35: NUMBER (%) OF DAILY SMOKERS, BY AGE, WHO MADE AT LEAST ONE QUIT ATTEMPT IN THE PAST 12 MONTHS (2004 – 2007)

Age group (years)	2004		2005		2006		2007	
	Number of smokers	%						
15-19	152,380	66.8%	148,410	63.4%	120,848	66.4%	133,084	68.6%
20-24	243,960	57.4%	207,020	50.9%	250,848	62.4%	226,263	59.7%
25-44	852,580	47.0%	917,490	51.0%	780,346	51.4%	820,104	51.1%
45+	533,520	39.0%	581,700	42.0%	608,076	38.1%	720,040	38.3%

Source: CTUMS (various years; with further calculations)<sup>508</sup>

## APPENDIX 36: SUMMARY OF THE NUMBER OF CLAIMS AND EXPENDITURES FOR NRT, BUPROPION, AND VARENICLINE

Quebec (All ages)	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008
<b>NRT Gum</b>					
Number of claims	7,063	6,746	9,741	12,523	13,860
Total cost to insurers	\$189,729	\$183,481	\$268,802	\$339,269	\$393,370
<b>NRT Patch</b>					
Number of claims	359,869	301,448	285,634	279,505	215,124
Total cost to insurers	\$11,119,990	\$9,367,015	\$8,903,802	\$8,778,351	\$7,217,607
<b>Bupropion</b>					
Number of claims	11,107	9,061	8,017	9,144	5,870
Total cost to insurers	\$452,688	\$370,100	\$326,427	\$354,796	\$247,168
<b>Varenicline</b>					
Number of claims	n/a	n/a	n/a	n/a	66,901
Total cost to insurers	n/a	n/a	n/a	n/a	\$3,153,632

NIHB	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008
<b>All ages*</b>					
<b>NRT Gum</b>					
Number of claims	3,233	3,692	3,892	4,449	4,669
Total cost to insurers	\$136,999	\$164,389	\$161,743	\$189,950	\$192,931
<b>NRT Patch</b>					
Number of claims	25,691	22,325	22,056	21,957	18,032
Total cost to insurers	\$1,945,763	\$1,664,499	\$1,699,763	\$1,658,601	\$1,276,879
<b>Bupropion</b>					
Number of claims	6,623	5,251	4,363	4,474	3,385
Total cost to insurers	\$454,982	\$381,193	\$317,575	\$334,643	\$256,214
<b>Varenicline</b>					
Number of claims	n/a	n/a	n/a	n/a	4,677
Total cost to insurers	n/a	n/a	n/a	n/a	\$341,039
<b>Age &lt; 18 years</b>					
<b>NRT Gum</b>					
Number of claims	218	168	155	82	89
Total cost to insurers	\$9,506	\$7,065	\$6,238	\$3,041	\$3,272
<b>NRT Patch</b>					
Number of claims	1,847	1,486	1,435	329	180
Total cost to insurers	\$152,804	\$114,402	\$117,481	\$26,678	\$14,159
<b>Bupropion</b>					
Number of claims	450	304	259	30	21
Total cost to insurers	\$32,624	\$23,112	\$19,970	\$1,890	\$1,465
<b>Varenicline</b>					
Number of claims	n/a	n/a	n/a	n/a	17

<b>NIHB</b>	<b>2003-2004</b>	<b>2004-2005</b>	<b>2005-2006</b>	<b>2006-2007</b>	<b>2007-2008</b>
Total cost to insurers	n/a	n/a	n/a	n/a	\$1,233
<b>Age 18-65 years</b>					
<b>NRT Gum</b>					
Number of claims	2,868	3,388	3,588	4,241	4,399
Total cost to insurers	\$121,123	\$151,684	\$149,416	\$181,616	\$183,318
<b>NRT Patch</b>					
Number of claims	23,033	19,895	19,802	20,751	17,014
Total cost to insurers	\$1,729,827	\$1,486,600	\$1,523,284	\$1,573,125	\$1,209,718
<b>Bupropion</b>					
Number of claims	6,006	4,772	3,989	4,331	3,287
Total cost to insurers	\$410,812	\$344,991	\$288,772	\$324,531	\$248,992
<b>Varenicline</b>					
Number of claims	n/a	n/a	n/a	n/a	4,448
Total cost to insurers	n/a	n/a	n/a	n/a	\$324,230
<b>Age &gt;65 years</b>					
<b>NRT Gum</b>					
Number of claims	119	125	144	126	181
Total cost to insurers	\$4,795	\$5,114	\$5,901	\$5,294	\$6,341
<b>NRT Patch</b>					
Number of claims	552	794	758	877	838
Total cost to insurers	\$40,745	\$50,136	\$52,487	\$58,798	\$53,002
<b>Bupropion</b>					
Number of claims	107	140	102	113	77
Total cost to insurers	\$7,194	\$10,054	\$7,350	\$8,222	\$5,757
<b>Varenicline</b>					
Number of claims	n/a	n/a	n/a	n/a	212
Total cost to insurers	n/a	n/a	n/a	n/a	\$15,576

\*Note that the sum of the number of claims in three age groups differed from the total FNIHB utilization shown in the main text because age groups were unknown for some data.

Source: Brogan Inc. Public and Private Drug Plan Databases.

## APPENDIX 37: AVERAGE COST PER CLAIM AND CHANGES IN THE NUMBER OF CLAIMS FOR NRT, BUPROPION, AND VARENICLINE (2004/2005 – 2007/2008)

Quebec (All ages)	Average cost per claim	% change from previous fiscal year				Average % change
		2004/05	2005/06	2006/07	2007/08	
<b>NRT Gum</b>	\$28	-4.5%	44.4%	28.6%	10.7%	19.8%
<b>NRT Patch</b>	\$31	-16.2%	-5.2%	-2.1%	-23.0%	-11.7%
<b>Bupropion</b>	\$41	-18.4%	-11.5%	14.1%	-35.8%	-12.9%
<b>Varenicline</b>	\$47	n/a*	n/a	n/a	n/a	n/a

\*Not applicable because only data in 2007/08 was reported.

## APPENDIX 38: ESTIMATED NUMBER OF CLAIMS AND COST PER CLAIM BY JURISDICTION<sup>§</sup>

Quebec	Predicted number of claims				Average cost per claim
	2007-2008	2008-2009	2009-2010	2010-2011	
<b>NRT Gum</b>	13,860	16,602	19,887	23,822	\$28
<b>NRT Patch</b>	215,124	190,030	167,863	148,282	\$31
<b>Bupropion</b>	5,870	5,111	4,451	3,876	\$41
<b>5% increase</b>	---	6,164	6,472	6,795	---
<b>10% increase</b>	---	6,457	7,103	7,813	---
<b>20% increase</b>	---	7,044	8,453	10,143	---
<b>30% increase</b>	---	7,631	9,920	12,896	---
<b>40% increase</b>	---	8,218	11,505	16,107	---
<b>50% increase</b>	---	8,805	13,208	19,811	---
<b>Varenicline</b>	66,901	---	---	---	\$47
<b>5% increase</b>	---	70,246	73,758	77,446	---
<b>10% increase</b>	---	73,591	80,950	89,045	---
<b>20% increase</b>	---	80,281	96,337	115,605	---
<b>30% increase</b>	---	86,971	113,063	146,981	---
<b>40% increase</b>	---	93,661	131,126	183,576	---
<b>50% increase</b>	---	100,352	150,527	225,791	---

New Brunswick	Predicted number of claims				Average cost per claim
	2007-2008*	2008-2009	2009-2010	2010-2011	
<b>NRT Gum</b>	1,326	1,588	1,902	2,278	\$40.49
<b>NRT Patch</b>	20,574	18,174	16,054	14,182	\$46.30
<b>Bupropion</b>	561	489	426	371	\$59.61
<b>5% increase</b>	---	589	619	650	---
<b>10% increase</b>	---	618	679	747	---
<b>20% increase</b>	---	674	808	970	---
<b>30% increase</b>	---	730	949	1,233	---
<b>40% increase</b>	---	786	1,100	1,540	---
<b>50% increase</b>	---	842	1,263	1,895	---
<b>Varenicline</b>	6,398	---	---	---	\$69.32
<b>5% increase</b>	---	6,718	7,054	7,407	---
<b>10% increase</b>	---	7,038	7,742	8,516	---
<b>20% increase</b>	---	7,678	9,214	11,056	---
<b>30% increase</b>	---	8,318	10,813	14,057	---
<b>40% increase</b>	---	8,958	12,541	17,557	---
<b>50% increase</b>	---	9,597	14,396	21,594	---

Ontario	Predicted number of claims				Average cost per claim
	2007-2008*	2008-2009	2009-2010	2010-2011	
<b>NRT Gum</b>	19,062	22,834	27,352	32,764	\$40.49
<b>NRT Patch</b>	295,872	261,359	230,872	203,941	\$46.30
<b>Bupropion</b>	8,073	7,030	6,122	5,331	\$59.61
<b>5% increase</b>	---	8,477	8,901	9,346	---
<b>10% increase</b>	---	8,881	9,769	10,746	---
<b>20% increase</b>	---	9,688	11,626	13,951	---
<b>30% increase</b>	---	10,495	13,644	17,737	---
<b>40% increase</b>	---	11,303	15,824	22,153	---
<b>50% increase</b>	---	12,110	18,165	27,248	---
<b>Varenicline</b>	92,013	---	---	---	\$69.32
<b>5% increase</b>	---	96,613	101,444	106,516	---
<b>10% increase</b>	---	101,214	111,335	122,469	---
<b>20% increase</b>	---	110,415	132,498	158,998	---
<b>30% increase</b>	---	119,617	155,502	202,152	---
<b>40% increase</b>	---	128,818	180,345	252,483	---
<b>50% increase</b>	---	138,019	207,029	310,543	---

Saskatchewan	Predicted number of claims				Average cost per claim
	2007-2008*	2008-2009	2009-2010	2010-2011	
<b>NRT Gum</b>	1,903	2,279	2,730	3,271	\$40.49
<b>NRT Patch</b>	29,535	26,090	23,046	20,358	\$46.30
<b>Bupropion</b>	806	702	611	532	\$59.61
<b>5% increase</b>	---	846	889	933	---
<b>10% increase</b>	---	887	975	1,073	---
<b>20% increase</b>	---	967	1,161	1,393	---
<b>30% increase</b>	---	1,048	1,362	1,771	---
<b>40% increase</b>	---	1,128	1,580	2,211	---
<b>50% increase</b>	---	1,209	1,813	2,720	---
<b>Varenicline</b>	9,185	---	---	---	\$69.32
<b>5% increase</b>	---	9,644	10,127	10,633	---
<b>10% increase</b>	---	10,104	11,114	12,225	---
<b>20% increase</b>	---	11,022	13,226	15,872	---
<b>30% increase</b>	---	11,941	15,523	20,180	---
<b>40% increase</b>	---	12,859	18,003	25,204	---
<b>50% increase</b>	---	13,778	20,666	31,000	---

<sup>§</sup>Predicted number of claims was calculated by multiplying the number of claims observed in 2007-2008 (Appendix 35) by the average annual % change in the number of claims from previous fiscal year shown in Appendix 36. In scenario 1, we assumed that current claim patterns for gum and patch, and bupropion continued and the number of claims of varenicline increased annually at the rate of between 5% and 50% from the 2007-2008 level. In scenario 2, we assumed that current patterns for the number of claims for gum and patch continued and the number of claims of varenicline and bupropion increased annually at the rate of between 5% and 50%.

\*Estimated number of claims had these drugs covered.

# APPENDIX 39: DATA EXTRACTION SHEET FOR QUESTIONS 11 AND 12

EXTRACTOR'S NAME:

First author, year of publication, (REFID)	Type of study	Data

# APPENDIX 40: SELECTED REPORTS FOR QUESTIONS 11 AND 12

