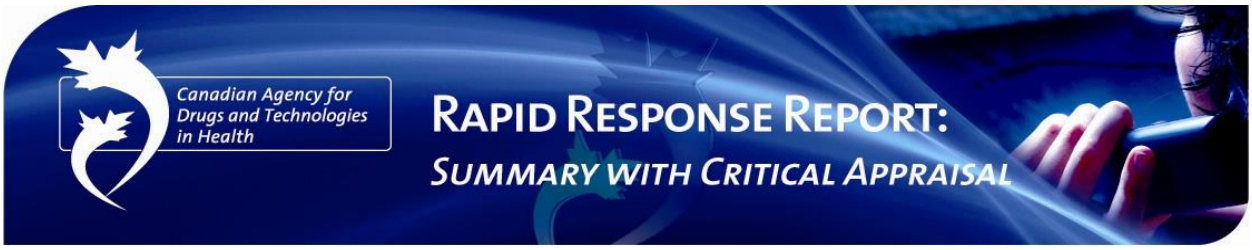

TITLE: Nicotine Replacement Therapy, Bupropion and Varenicline for Tobacco Cessation: A Review of Clinical Effectiveness

DATE: 8 March 2016

CONTEXT AND POLICY ISSUES

Tobacco use, including smoking and oral tobacco, is a main preventable cause of morbidity and death worldwide.[1] Smokeless tobacco consumption has adverse health outcomes as well, including a risk for periodontal disease, high heart rate and blood pressure, oral cancer, and other cancers, such as kidney and pancreatic.[2] Tobacco contains nicotine, which is an addictive chemical component, and attracts tobacco users.[1] While some tobacco users may report quitting unaided, interventions for tobacco cessation are important in enabling tobacco users to stop using. These interventions include pharmacological and behavioural approaches. Behavioural approaches may include interventions such as counselling and education to aid tobacco cessation.

Three pharmacological approaches to tobacco smoking cessation, nicotine replacement therapy (NRT), bupropion, and varenicline, are considered in this review. NRT delivers non-toxic forms of nicotine to help tobacco users deal with nicotine cravings; as NRT does not contain the other toxic compounds found in cigarettes and other tobacco products, it preferred to tobacco use.[1] NRT maintains stimulation of the nicotine receptors.[1] Forms of delivery for NRT include: nicotine gum, nicotine lozenge, nicotine patch, nicotine inhaler, nicotine spray, and nicotine sublingual tablets.[1]

Bupropion is an antidepressant.[1,3] Antidepressants are thought to aid smoking cessation in three ways; depressive symptoms may be produced due to nicotine withdrawal, nicotine may have an antidepressant effect, and antidepressants may affect neural pathways of nicotine addiction.[3]

Varenicline is a nicotine receptor partial agonist.[1,4] It reduces the pleasure and craving for nicotine.[4] Nicotine receptor partial agonists act by maintaining levels of dopamine to mitigate withdrawal symptoms and reduce the satisfaction of smoking.[4] In this way, varenicline and other nicotine receptor partial agonists aid in tobacco cessation.

This review aims to address questions of clinical effectiveness for NRT, bupropion, and varenicline in the general population of tobacco users. The findings of this report should be considered in the context of the previous CADTH Health Technology Assessment (HTA) on the subject, which employed a more thorough methodology and analysis of the primary studies on this topic.[1]

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of nicotine replacement therapy versus bupropion or varenicline in the general population of tobacco users?

2. What is the comparative clinical effectiveness of nicotine replacement therapy, bupropion or varenicline versus placebo in the general population of tobacco users?

KEY FINDINGS

Ten relevant studies are included in this review. The clinical effectiveness of nicotine replacement therapy (NRT) compared to bupropion was found to be similar. Studies that compared varenicline to NRT reported higher rates for abstinence for participants in the varenicline group. There is some evidence to suggest that participants using bupropion, and those using varenicline achieved higher rates of abstinence when compared to placebo. Findings for NRT versus placebo or control were mixed, with some studies reporting no difference and one study reporting higher rates of abstinence for those on NRT.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and January 14, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Smokers of any age in the general population[a]
Intervention	Q1: Nicotine replacement therapy products (e.g., patches, gum, inhaler, lozenges, sublingual tablets) Q2: Nicotine replacement therapy products, bupropion, varenicline
Comparator	Q1: Bupropion or varenicline Q2: Placebo
Outcomes	Clinical effectiveness (e.g., smoking cessation, smoking reduction, quantity of quit attempts required, interval between quit attempts); Harms (e.g., adverse events, abuse potential, diversion)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs) (if few relevant HTAs, SRs and MAs are identified)

[a] The definition for general population was considered to be individuals of any ethnicity, sex, or age, undergoing treatment for the first time or for re-treatment, and considered "relatively healthy."[1]

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Due to the volume of literature, individual randomized controlled trials were excluded from the final report. Only the most recent version of a systematic review was included. Systematic reviews (SRs) were excluded if a more recent SR or SRs included the same studies.

Additionally, studies of special populations were not included in this report, and considered to be pregnant women, persons with mental illness, and persons with chronic obstructive pulmonary disease, cardiovascular disease, or diabetes. SRs were excluded if less than 50% focused on the general population.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR Checklist.[5] The included network meta-analysis (NMA) was also critically appraised using the International Society For Pharmacoeconomics and Outcomes Research checklist.[6,7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 558 citations were identified in the literature search. Following screening of titles and abstracts, 531 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. Of the potentially relevant articles, 10 studies were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

A summary of the study characteristics can be found in Table A1 in Appendix 2.

Study Design

Nine of the included studies[2-4,8-13] were SRs, and the remaining study[14] was a NMA.

Designs of Included Studies in the Systematic Reviews

The SRs included primarily randomized controlled trials (RCTs), however, two[2,4] included open-label studies. The total number of studies included in the SRs varied widely, from a total of three studies[8] to 150.[13]

Four of the SRs required that the included studies had a follow-up period of at least six months.[3,9,10,13] Other follow-up times also were used, including: 12 and 26 weeks;[8] four, six, eight, ten and 12 weeks;[2] 24 weeks;[4] and 26 weeks, greater than three months and six months.[11]

Country of Origin

The country of origin for the included SRs was determined by the country of the primary author. Five studies[2,3,8,9,14] were from the United States, and four studies[4,10,11,13] were from the United Kingdom, and one study[12] was from Canada.

Patient Population

Two of the SRs[2,11] examined interventions for smoking cessation in adolescent or young smokers. Ages of participants ranged from 11 to 21 years in one review[2] and 13 to 17 years in the other review.[11]

Two of the SRs[8,9] examined interventions for smokeless tobacco users. The majority of participants in these reviews were male. Ages of participants in these reviews ranged from 31[9] to 43.9 years old.[8,9]

The SR by Hughes[3] examined antidepressants, including bupropion, for smoking cessation. Participants varied by setting (e.g., community and hospital) and demographic information. The average age of participants for the included studies that reported on age ranged from 36 to 53 years, and it also included two studies reporting on adolescents with the average ages reported as 16 and 17 years. The sex in the included primary studies varied from 100% female to 100% male.[3]

The NMA by Mills 2014[14] examined cardiovascular events associate with pharmacological interventions for smoking cessation. Participants also varied by demographic characteristics. Sex varied by study, from studies that were 100% female to 100% male. Average age of participants in studies that reported on age also differed, from an average of 16 to 61 years.[14]

The SR by Hajek[10] examined relapse prevention interventions for smoking cessation. Participants were considered for inclusion if they had quit smoking on their own, if they were undergoing enforced abstinence, or if they were undergoing treatment programs for initial cessation.[10] The average age of participants in the included studies that reported on age ranged from 40 to 46 years. Sex also varied by the studies and ranged from 22% to 57% female.[10]

The SR by Cahill[4] examined nicotine receptor partial agonists as interventions for smoking cessation. The average age of participants in the included studies that reported on age ranged from 39 to 51 years. Sex also varied by the studies and ranged from 3% to 51% female.[4]

The SR by Mills 2012[12] examined pharmacological interventions for smoking cessation. The demographic characteristics of the included studies were insufficiently reported and the study authors did not present the ages or sex of the participants in the included studies, though it was reported that the study authors collected this information.

The SR by Stead[13] examined NRT for smoking cessation. The average age of participants was typically between 40 and 50 years, and one included study reported on adolescents. The sex in the included primary studies varied from 100% female to 100% male.[13]

Interventions and Comparators

The included reviews looked at the following interventions and comparators:

- NRT versus bupropion[3,12-14]
- NRT versus varenicline[4,12,14]
- Bupropion versus placebo[3,9-11,14]
- NRT versus placebo[2,9-11,13,14]
- Varenicline versus placebo[4,8-10,14]

Behavioural interventions were also used by some of the included studies in the SRs. For example, all included studies in the SR by Schwartz[8] included a behavioural counselling component.

Outcomes

The included reviews considered the following outcomes:

- Adverse events[3,4,8,11,13,14]
- Smokeless tobacco abstinence[8,9]
- Unspecified or all tobacco abstinence[4,8,10]
- Smoking cessation[2,3,11-13]
- Reduction in greater than 50% of cigarettes consumed[3]

The definition of smoking or tobacco cessation differed across the studies included in the SRs. It was measured as a point prevalence of abstinence, where abstinence occurred either at prolonged or multiple points during the study period, but not necessarily since the beginning of treatment.[2,8,10,11] Biochemical verification of tobacco or smoking abstinence, such as exhaled carbon monoxide, was also reported by some of the SRs.[2,3,9,11]

Summary of Critical Appraisal

A summary of the critical appraisal can be found in Table A2 in Appendix 3.

Overall, the ten studies included in this review were of moderate to high quality. Six of the ten included SRs[3,4,9-11,13] were Cochrane reviews. These reviews described the objectives, methods and results; for example, all included a list of included and excluded studies, study findings, and funding sources of the included studies. These SRs performed comprehensive search

strategies of multiple databases. In addition, most synthesized the data by means of meta-analysis, and when meta-analysis was not appropriate (e.g., one study per outcome, or reporting on adverse events that were not systematically reported by included studies) a narrative synthesis was used. The quality of the included studies was also examined with a risk of bias tool, reported, and used appropriately in the formulation of the review conclusions. However, the review by Ebbert[9] perhaps inappropriately pooled the results of the NRT therapies regarding tobacco abstinence at six months or greater. For instance, a sensitivity analysis of removing the NRT lozenge studies rendered the results of that estimate as not significant (p-values or confidence intervals [CIs] not reported). Publication bias was either not mentioned at all or insufficiently reported across many of the studies.[2,4,9-12] Studies that performed publication bias analyses (i.e., funnel plots) or determined that they could not assess publication bias (i.e., fewer than ten studies) were few.[3,8,13] Though funnel plots were not always shown, the authors stated that there was no evidence of publication bias.[3]

The SR by King[2] did not provide a list of included and excluded studies, a prior design was uncertain, and duplicate screening of the literature and data extraction was uncertain.[2]

The SR by Schwartz[8] used statistically validated methods (i.e., I^2) for assessing heterogeneity and then used a random-effects model in their meta-analysis. However, it was uncertain if their literature search was comprehensive as it did not contain some commonly used terms for smokeless tobacco, such as snus.[8] Additionally, women were underrepresented in the studies (ranged from 0% to 10.5% female), so the generalizability of the results to this population are questionable.[8]

The relevance of the NMA by Mills[14] may be limited as it reported on cardiovascular outcomes only. Although the NMA was a complete and closed network, its credibility is questionable due to the quality of the included studies in the network. Furthermore, the reporting of the review lacked clarity around its consistency as a network. [14]

The 2012 study by Mills[12] had a comprehensive literature search, study selection and data extraction was done in duplicate, study characteristics were reported, and appropriate statistical measures used to assess and account for heterogeneity. In terms of limitations, the evaluation of individual study quality was not reported, excluded studies were not provided, and it was uncertain whether a prior design was used.

Summary of Findings

A summary of the findings of the included studies can be found in Table A3 in Appendix 4.

What is the comparative clinical effectiveness of nicotine replacement therapy versus bupropion or varenicline in the general population of smokers?

<u>NRT versus Bupropion:</u>

Four studies reported results on NRT versus bupropion.[3,12-14] These reviews found NRT and bupropion to be of similar clinical effectiveness.[3,12,13] One SR reported that bupropion may be more effective than standard-dose nicotine patch at four weeks, while a high-dose nicotine patch may be more effective than bupropion at six months.[12] There were few adverse cardiovascular events on either drug; though those on NRT may experience a higher risk of cardiovascular events and those on bupropion may experience a protective effect.[14]

The SR by Hughes[3] found bupropion to be of a similar efficacy to NRT. Quit rates for the placebo group ranged from 0% to 33%, and for the bupropion group rates ranged from 4% to 43%.[3] Stead[13] reported no significant difference in the efficacy of NRT versus bupropion. The 2012 study by Mills[12] found standard-dose nicotine patch (≤ 22 mg) and bupropion to be of a similar efficacy in a random-effects multiple treatment comparison analysis at several follow-up time points, but bupropion to be favourable in the short-term (i.e., four weeks).[12] This study[12] found high-dose nicotine patch (> 22 mg) to be slightly favourable over bupropion, but only significant at six months.

The NMA by Mills[14] reported on cardiovascular events (CV) and major adverse cardiovascular events (MACE) for NRT versus bupropion; this included results from three RCTs. Few events, both CV and MACE, were experienced by patients on bupropion and NRT. The study authors found no increase in CV events for participants using bupropion, but indicated that the risk of CV events was elevated for those on NRT. This observation was predominately due to less serious events. There was no clear risk for MACE for participants on NRT, but there was some protective effect for participants on bupropion. The cause of this effect was preliminary and not well understood.[14]

NRT versus Varenicline:

Three included reviews reported results for NRT versus varenicline.[4,12,14] These studies found participants on varenicline were more likely to be abstinent from tobacco when compared to participants using NRT[4,12] though this result was not always significant.[4] Few reports of adverse cardiovascular events on either drug were found.[14]

The SR by Cahill[4] included two open-label trials (n = 778) of varenicline versus NRT. These studies showed a marginal advantage of varenicline over NRT, though neither were significant.[4] The 2012 SR by Mills[12] found varenicline had significantly greater smoking abstinence rates over other interventions (e.g., control, standard-dose NRT, high-dose NRT, combination NRT, and bupropion), with the exception of high-dose nicotine patch or combination NRT at six months. This study found that varenicline had the highest probability of being the best treatment at all time points (e.g., short-term, three months, six months, and 12 months).[12]

The SR by Mills[14] reported on CV events and MACE for NRT versus varenicline; this included results from one RCT. Few events, both CV and MACE, were experienced by patients on varenicline and NRT.[14] There was no significant difference in rates of CV events or MACE for varenicline versus NRT.

What is the comparative clinical effectiveness of nicotine replacement therapy, bupropion or varenicline versus placebo in the general population of smokers?

Bupropion versus Placebo:

Five of the included studies reported on bupropion versus placebo.[3,9-11,14] Results for this comparison were mixed, with three studies reporting no difference in abstinence for bupropion versus placebo[9-11] however, one NMA reported greater abstinence for study participants on bupropion versus placebo.[3] The authors indicated that bupropion seemed to be protective against the risk of MACE.[14]

For all tobacco abstinence at six months or greater, the SR by Ebbert[9] regarding smokeless tobacco cessation did not find a significant difference between bupropion versus placebo. This result was similar to the finding in the SR by Hajek[10] which at 12 months found similar rates of abstinence for those on bupropion versus placebo. For adolescent smoking cessation, the study by Stanton[11] found one study that compared bupropion to placebo; there was no significant difference for bupropion versus placebo.

The SR by Hughes,[3] which included 44 studies and 13,728 participants, found bupropion to be more effective than placebo for abstinence at six months or greater. This result was also seen at 12 months of follow-up, which found bupropion to be more effective.[3]

In the pair-wise analysis of CV events by Mills, there was no significant difference for bupropion versus placebo. The results were similar for rates of MACE, with bupropion versus placebo showing no significant difference.[14] The NMA reported no significant difference of all CV events for bupropion versus placebo; however, there were fewer MACE on bupropion versus placebo which was significantly different.[14]

In one trial of bupropion intervention for adolescents, 4% of patients reported AEs, and eight patients dropped out of the trial due to AEs.[11] Two serious AEs occurred in this trial. One participant intentionally overdosed on a combination of study medication and other substances and required hospitalization. The other was hospitalized after ingesting another toxic substance.[11]

NRT versus Placebo:

Six SRs reported on NRT compared to placebo.[2,9-11,13,14] There was little evidence to suggest that NRT was more effective than placebo,[2,9-11] with the exception of one study[13] where NRT was found to improve rates of abstinence. Compared to placebo, the risk of CV events was significantly more for patients on NRT, though this was not significant for MACE.[14]

For adolescent smoking cessation, the SR by King[2] reported the proportion of participants who were abstinent or experiencing a decrease in cigarettes per day at the end of treatment. There was little evidence to suggest that NRT was more effective than placebo; abstinence or decrease in smoking ranged from 10.2% to 45.0% on patch, and 47.2% on gum, versus 4.1% to 46.6% on placebo.[2] This was similar for the SR by Ebbert[9] which reported on interventions for smokeless tobacco. There was no significant different for patch or gum versus placebo.[9] While lozenge appeared to be more effective than placebo, three lozenge trials without placebo control were included in this analysis.[9] When pooled, all NRT performed better than placebo; however this result was not significant when the lozenge trials without placebo controls were removed.[9]

The SR by Hajek[10] reported on one trial each for NRT gum versus placebo, and NRT inhaler versus placebo. Neither trial found a significant difference for the NRT therapy versus placebo at 12 months or greater.[10] Similar results were reported in the SR by Stanton[11] which also reported one trial on NRT patch versus placebo, and NRT gum versus placebo. The authors reported that this study was underpowered to have adequately detect a difference between rates of abstinence for NRT versus placebo if one does exist.[11]

Contrary to the other SRs, the review by Stead[13] found that NRT in any form (e.g., gum, patch, oral tablets/lozenges, oral spray, nasal spray, and inhalers) was more effective than placebo for rates of abstinence.[13]

In a pairwise-comparison by Mills, there were significantly more CV events for those on NRT versus placebo; this was not similar for MACE, with no significant difference for those on NRT versus placebo.[14] The NMA reported a significant difference of all CV events for NRT versus placebo; however, there was no difference in risk of MACE for those NRT versus placebo.[14]

Varenicline versus Placebo:

There were five studies that reported findings for varenicline versus placebo.[4,8-10,14] It was uncertain whether varenicline improved abstinence for smokeless tobacco users.[8,9] Varenicline improved abstinence, compared to placebo, for smokers undergoing relapse prevention[10] and for smokers, in general.[4] There were no significant differences in terms of CV events or MACE for varenicline versus placebo.[14] Though other adverse events, such as nausea, may be experienced by those on varenicline.[4]

For patients using smokeless tobacco, the rates of tobacco abstinence was higher for patients on varenicline versus placebo at six months in the SR by Ebbert.[9] The SR by Schwartz[8] did find varenicline (48% seven-day point-prevalence abstinence) to be effective at 12 weeks when compared to placebo (33% seven-day point-prevalence abstinence). These rates of abstinence, however, may not be significantly different over time. Schwartz[8] found that there was no significant difference at 26 weeks for varenicline (49% seven-day point-prevalence abstinence) versus placebo (30% seven-day point-prevalence abstinence). Based on the findings in one study, varenicline was found to improve abstinence for patients undergoing treatment for relapse prevention.[10] In their review of nicotine receptor partial agonists, Cahill[4] found standard-dose, as well as lower and variable dose, varenicline to be effective compared to placebo for continuous or sustained abstinence at six months or longer.

Increased rates of nausea for patients on varenicline was reported by Cahill,[4] with rates ranging from 17% to 44% of patients. Trials with lower than standard doses of varenicline reported lower rates of nausea.[4] The risk of nausea, insomnia, abnormal dreams (undefined) and headache was significantly higher for varenicline versus placebo.[4] However, the risk of nausea and sleep disturbance for the comparison of varenicline versus placebo was not significant in the SR by Schwartz.[8] The incidence of mood disturbances may be lower for those in the varenicline group versus placebo, but again, this was not significant.[8] In both the pairwise meta-analysis, and the NMA by Mills,[8] the risk of CV and MACE was not significantly different for varenicline versus placebo.

Other Harms:

The SR by Hughes[3] reported on AEs for patients on bupropion. It was not possible from the pooled result to determine the comparator of the included studies. In general, the review found that insomnia, dry mouth, and nausea were the most common side effects. Allergic reactions have also occurred on bupropion, and at a rate of about one to three patients per 1000.[3] There were no significant differences of serious AEs for bupropion versus placebo/control groups.[3]

The SR on NRT by Stead[13] also reported on AEs, but did not attempt to systematically synthesize the information. The authors reported that the side effects were mild, in general.

Common side effects for nicotine gum included gastrointestinal disturbances, hiccoughs, jaw pain, and orodental problems, and common side effects for the patch were skin irritation and sensitivity. These side effects may have impacted up to 54% of patch users, but was typically mild. Inhalers, nasal and oral sprays had side effects related to irritation at the site of administration (e.g., nose and mouth), but coughing, oral burning and throat irritation were alsoreported. Runny nose and nasal irritation were most common for nasal sprays.[13] Stead attempted to replicate the results from Mills[14] on cardiovascular events and reported a similar odds of CV for patients on NRT compared to placebo, which was significant (odds ratio = 1.88; 95% confidence interval 1.37 to 2.57).

Limitations

This review was limited to outcomes and populations reported in the SRs given the large volume of high quality evidence available on this topic. The discussions and analyses on the baseline smoking or tobacco habits of the study populations in the included SRs was insufficient. It is possible that some interventions may perform better than others, depending on the tobacco habits of the individuals, but these results were not reported. Additionally, smoking cessation is often self-reported and may overestimate the success of individuals participating in smoking cessation programs. This outcome is often measured as point prevalence versus continuous treatment from the beginning of the study. Some trials, however, did require biochemical verification of smoking cessation (e.g., exhaled carbon monoxide). Also, any reports of AEs may be due to nicotine withdrawal (e.g., a physical dependence) rather than the pharmacological intervention used.[3]

It is important to note that while the SRs reported on the aforementioned interventions and comparators, the primary studies included in their analyses were often coupled with behavioural therapies for smoking cessation (e.g., counselling, information). Reporting on the efficacy of behavioural interventions was outside the scope of this report. The efficacy of the interventions alone is uncertain, and potentially confounded by the use of behavioural therapies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The findings of this report should be considered in the context of the previous CADTH HTA on the subject, which employed a more thorough methodology and analysis of the primary studies on this topic.[1] The HTA found that varenicline was superior to bupropion and conventional use of the nicotine patch, and that all pharmacotherapies included in the HTA were efficacious in aiding the general population to quit smoking.[1] The current review gives an overview of the recent evidence published since this HTA, and provides areas for consideration within the body of evidence on this subject, including the previous CADTH HTA. Regarding NRT versus placebo, most studies published between 2012 and 2016 showed no difference in tobacco related outcomes, but the research was conducted in specific sub-populations (e.g., adolescents, smokeless tobacco users, or persons who had previously quit and were preventing relapse) and may be less relevant to the general population of smokers. The findings and recommendations of the HTA are still considered relevant.

Ten relevant studies are included in this review. The findings suggest that varenicline groups achieved higher rates of abstinence compared to both NRT and placebo, bupropion and NRT were of similar effectiveness, and bupropion and varenicline both had higher abstinence rates compared to placebo. The number of SRs that reported adverse events in any of the treatment

groups was six. When side effects did occur, they were usually mild in presentation and localized (e.g., skin irritation from the nicotine patch).

It is uncertain how much these findings of clinical effectiveness were influenced by the baseline characteristics of the study participants (e.g., how many cigarettes they smoked per day prior to therapy), as well as the differences among the behavioural therapies being offered along with the pharmacological therapies. These behavioural interventions differed across the studies, as therapies counselling and information presented as a booklet. Many smoking and tobacco cessation programs offer a combination of behavioural and pharmacological interventions.[1] The success of these cessation programs may depend on the type of treatment being offered.

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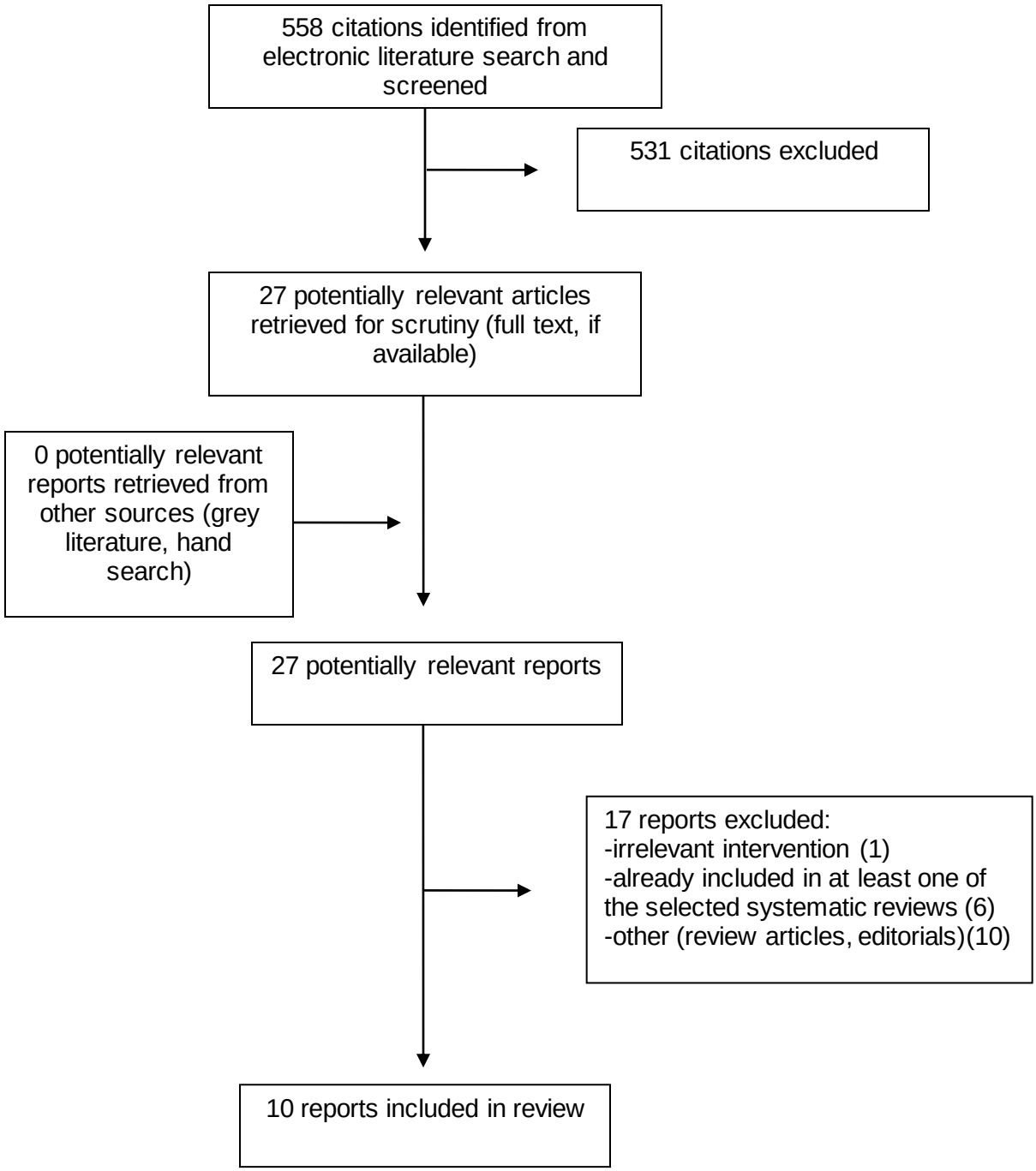
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Search Databases and Dates	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
King, 2016, USA[2]	EBSCOhost, ERIC, ProQuest, and PubMed, no dates reported	8 studies; 6 RCTs, 2 non-randomized OL[a]	High school students (6 studies), students with psychiatric conditions (1 study),[b] students not attending school (1 study) Number of participants: range: n = 22 to n = 257; mean of all studies: n = 127 RCTs only: n = 98 to n = 257	OL studies: Nicotine patch (6-8 weeks) and counselling RCTs: Nicotine patches (6–12 weeks) + behavioural component (3 studies); nicotine patch or gum + CBT (4 or 12 weeks; 2 studies); nicotine patches alone (1 study)	Placebo (3 RCTs); patch + bupropion (1 RCT)[c]; nicotine gum, placebo (2 RCTs); no comparator (2 non-randomized OL)	Smoking abstinence: Self-reported at 7 days with CO ≤ 5 to 9 ppm (3 RCTs); CO (cutoff NR; 1 RCT); Self-report (prolonged abstinence; 1 RCT); Self-reported reduction in CPD + CO (no cutoff; 1 RCT); Self-reported a 7 days CO ≤ 8 ppm (2 non-randomized OL) Follow-up: 4 weeks (2 RCTs); 6 weeks (1 OL); 8 weeks (1 OL); 10 weeks (3 RCTs); 12 weeks (1 RCT)
Schwartz, 2016, USA[8]	PubMed, EMBASE, clinicaltrials.gov, Cochrane Registry, all studies published up to February 1, 2014	3 RCTs	Number of participants: range: n = 76 to n = 431; total n = 744	Varenicline plus behavioural counselling (12 weeks of treatment)	Placebo	Tobacco abstinence: 7-day PP of SLT abstinence after 12 and 26 weeks of

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Search Databases and Dates	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
			Mean Age, years: range: 34.2 to 43.9 Male: range: 89.5% to 100%			treatment; Adverse events (mood disturbance, nausea, sleep disturbance)
Ebbert, 2015, USA[9]	Cochrane Tobacco Addiction Group specialised register (which includes Cochrane Central Register of Controlled trials, PsychINFO, EMBASE, MEDLINE) in June 2015; previous versions of this review also included, Web of Science, Dissertation Abstracts Online, Scopus, Healthstar, ERIC, National Technical Information Service database, Current Contents	34 trials (16 trials of relevant intervention and comparator)	Number of participants: n = 3722 (bupropion studies, n = 293; NRT studies, n = 2922; varenicline studies, n = 507)	Bupropion (2 studies); nicotine patch (5 studies); nicotine gum (2 studies); nicotine lozenge (5 studies); varenicline (2 studies)	Placebo; no placebo (3 lozenge studies)	All tobacco or SLT abstinence at least 6 months follow-up; all but two lozenge studies required biochemical verification (e.g., exhaled CO)
Hughes, 2014, USA[3]	Cochrane Tobacco Addiction Group's Specialised Register (which includes Cochrane Central Register of Controlled trials, MEDLINE, EMBASE, and PsycINFO), reviews and meeting abstracts in July 2013	90 trials (52 trials of relevant intervention and comparator[d])	Number of participants: bupropion vs. placebo, n = 13,728; bupropion vs. NRT, n = 4086	Bupropion	Placebo or no pharmacologic control (44 studies); NRT (8 studies)	Tobacco abstinence at least 6 months follow-up; biochemical verification if reported (e.g., exhaled CO) Adverse events

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Search Databases and Dates	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Mills, 2014, USA[14]	MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info, and Web of Science from inception to March 20, 2013. Bibliographies of published SRs and HTAs, contacted study authors of RCTs.	63 RCTs total	Total number of participants: n = 30,508	NRT (21 studies); bupropion (27 studies); varenicline (18 studies)[e]	Placebo; NRT	Cardiovascular events and major cardiovascular events
Hajek, 2013, UK[10]	Cochrane Tobacco Addiction Group register (which includes Cochrane Central Register of Controlled trials, MEDLINE, EMBASE, and PsycINFO) in May 2013	63 trials total	Smokers undergoing relapse prevention Number of participants: NRT trials, n = 553; bupropion trials, n = 1697; varenicline trials, n = 1210	NRT (2 trials); bupropion (6 trials); varenicline (1 trial)	Placebo	Prolonged or multiple PP tobacco abstinence at least 6 months follow-up
Stanton, 2013, UK[11]	Cochrane Tobacco Addiction Group Specialized Register (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and PsycINFO) in February 2013	28 trials total (2 trials with relevant comparator and intervention)	Adolescent smokers, age range 13 to 17 years Number of participants: NRT trial, n = 120; bupropion trial, n =	NRT including both gum and patch (1 trial); bupropion	Placebo	NRT: Self-reported 7-day PP abstinence, CO, salivary cotinine and thiocyanate at > 3 months and 6 months

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Search Databases and Dates	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
			312			Bupropion: Self-reported 7-day PP abstinence and exhaled CO at 26 weeks Adverse events
Cahill, 2012, UK[4]	Cochrane Tobacco Addiction Group register (which includes Cochrane Central Register of Controlled trials, MEDLINE, EMBASE, and PsycINFO) in December 2011	24 RCTs (17 trials of relevant intervention and comparator)	Total number of participants: n = 8,100	Varenicline	placebo (15 studies) NRT (2 studies)	Varenicline vs placebo Sustained abstinence at longest follow-up (at least 24 weeks) Abstinence for long-term (52 weeks) use of varenicline Varenicline vs NRT Point prevalence abstinence at 24 weeks Adverse events
Mills, 2012, Canada[12]	MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info, Web of	146 RCTs (unclear number with relevant comparator)	Smokers, unclear total number of patients for studies included in the MTC	Standard dose nicotine patch (≤ 22 mg), high dose nicotine patch (> 22 mg)	Varenicline, bupropion	Smoking abstinence in the short term (not defined), 3 months, 6 months, and 12 months as assessed by a random-effects

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Search Databases and Dates	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Science, OVID, ScienceDirect, and Ingenta from inception to January 1, 2012. Bibliographies of published SRs and HTAs searched.					MTC meta-analysis
Stead, 2012, UK[13]	Review update: Cochrane Tobacco Addiction Group Specialized Register (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and PsycINFO in July 2012. Original review also searched Cancerlit, Health Planning and Administration, Social Scisearch, Smoking & Health and Dissertation Abstracts up to December 1996.	150 RCTs and quasi-randomized trials: NRT vs. placebo/no NRT (117 trials); NRT vs. bupropion (5 trials)	Cigarette smokers, average age 40 to 50 years Number of participants: NRT vs. placebo/no NRT, n = 51 265; NRT vs. buproprion, n = 4470	NRT (including chewing gum, transdermal patches, nasal and oral spray, inhalers and tablets or lozenges)	Placebo or no NRT control; buproprion	Abstinence at 6 months or longer (6–24 months follow up) Adverse events

CBT = cognitive behavioural therapy; CO = carbon monoxide; CPD = cigarettes per day; HTA = health technology assessment; MTC = multiple treatment comparison; NR = not reported; OL = open-label; PP = point prevalence; RCT = randomized controlled trial; SLT: smokeless tobacco; SR = systematic review; UK = United Kingdom; USA = United States of America; vs. = versus.

[a] Open-label studies did not fit the inclusion criteria for this report as there was no comparator group

[b] Students with psychiatric conditions did not fit the inclusion criteria for this report as they were not considered general population

[c] This RCT did not fit the inclusion criteria for this report due to this comparator

[d] This includes trials of special populations such as patients with psychiatric conditions, comorbidities, etc.

[e] Some RCTs included more than one intervention

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR Checklist[5] link to AMSTAR checklist

Strengths	Limitations
King[2]	
• The quality of the included studies was assessed and documented • The literature search included multiple databases	• A priori design is uncertain as there was no mention to it, or to a published protocol, which raises the question of selective reporting • Uncertain whether there was duplicate screening of the literature and duplicate data extraction • A list of included and excluded studies was not provided • Publication bias was not assessed or mentioned if it was not appropriate to assess publication bias • Important participant characteristics (i.e., race) were not reported • There was no reported search of the grey literature or unpublished literature
Schwartz[8]	
• Study protocol was referenced and available online • Study selection and data extraction was done in duplicate • Statistical heterogeneity between trials was assessed using the I^2 statistic • Random effects model of meta-analysis was performed due to statistical heterogeneity • Publication bias was appropriately not performed as there were less than 10 included studies	• Search strategy was limited in search terms (did not include the term snus) • There was no reported search of the grey literature or unpublished literature • Women were underrepresented in the included studies, and the efficacy of varenicline in this population is uncertain • A list of included and excluded studies was not provided
Ebbert[9]	
• Review included a list of included and excluded studies, funding sources of included studies, and detailed methodology • The characteristics of the included studies were provided • Comprehensive search strategy, including a search for unpublished literature • Final study selection and data extraction were done in duplicate • Statistical heterogeneity between trials was assessed using the I^2 statistic • Heterogeneity was appropriately a determining factor in the use of a random-effects meta-analysis or a fixed-effects meta-analysis	• Initial screening of the literature search was not done in duplicate • Pooling of the NRT lozenge trials may not have been appropriate, as sensitivity analysis revealed that the three lozenge trials without placebo affected significance of the result (no longer was significant) • Publication bias was not assessed or mentioned if it was not appropriate to assess publication bias (i.e., less than 10 studies), though noted as a possible limitation of the review
Hughes[3]	
• Review was well reported, including a list of included and excluded studies, funding sources of included studies, and detailed methodology	• Initial screening of the literature search was not done in duplicate • While funnel plots were done to assess

Table A2: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR Checklist[5] link to AMSTAR checklist

Strengths	Limitations
• The characteristics of the included studies were provided • Comprehensive search of the published literature • Statistical heterogeneity between trials was assessed using the I^2 statistic • The quality of the included studies was assessed and documented	publication bias, these were not shown and poorly reported
Mills, 2014[14]	
• Included multiple databases in their search of the literature • List of excluded studies in supplemental tables available online • Trials form one connected network, providing credibility to this study • Separate analysis was performed for high-risk patients • Random-effects model was used and an appropriate analysis to deal with heterogeneity • Individual study results are reported	• No apparent search of the grey literature • Relevance of the NMA is limited, as it reports only on adverse cardiovascular events • Demographics of the patients from the included studies is poorly reported (e.g., race is missing, pre-existing medical conditions generally reported) • Studies of variable quality were included in the network, giving question to credibility • Bias related to the selective reporting of cardiovascular events by the included studies is possible, giving question to credibility • Consistency between comparisons was not discussed
Hajek, 2013[10]	
• Review included a list of included and excluded studies, funding sources of included studies, and detailed methodology • The characteristics of the included studies were provided • Comprehensive search of the literature • Statistical heterogeneity between trials was assessed using the I^2 statistic • In the presence of significant heterogeneity (I^2 > 50%) pooled estimates were not reported • The quality of the included studies was assessed and documented	• Publication bias was not assessed or mentioned if it was not appropriate to assess publication bias (i.e., less than 10 studies)
Stanton, 2013[11]	
• Review included a list of included and excluded studies, funding sources of included studies, and detailed methodology • The characteristics of the included studies were provided • Comprehensive search of the literature • Duplicate study selection and final study inclusion • The quality of the included studies was assessed and documented	• Publication bias was not assessed or mentioned if it was not appropriate to assess publication bias (i.e., less than 10 studies) • No justification was provided for the exclusion of studies with follow-up of less than 6 months • Uncertain if duplicate data extraction happened

Table A2: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR Checklist[5] link to AMSTAR checklist

Strengths	Limitations
Cahill, 2012[4]	
• Review included a list of included and excluded studies, funding sources of included studies, and detailed methodology • The characteristics of the included studies were provided • Comprehensive search of the literature • Statistical heterogeneity between trials was assessed using the I^2 statistic • Heterogeneity was appropriately a determining factor in the use of a random-effects meta-analysis or a fixed-effects meta-analysis • The quality of the included studies was assessed and documented	• Publication bias was not assessed or mentioned if it was not appropriate to assess publication bias (i.e., less than 10 studies) • Uncertain if duplicate study selection and data extraction happened
Mills, 2012[12]	
• Study selection and data extraction performed in duplicate • Comprehensive literature search of multiple databases and hand-searching performed • Study characteristics tables provided in an appendix • Appropriate statistical measures used to assess and account for heterogeneity (I^2, random-effects model) • Conflicts of interest for review authors was explicit	• Unclear whether a priori design was used; no reference to a published protocol or objectives • Unclear use of publication status as a literature search and study inclusion criterion • Excluded studies list not provided • Evaluation of individual study quality described in the methods, but results not reported (summary of overall quality only) • Limitations of included study quality not explicitly addressed in conclusions • Likelihood of publication bias discussed, but graphical or statistical assessments not provided • Conflicts of interest for included studies not provided
Stead, 2012[13]	
• Review included a list of included and excluded studies, funding sources of included studies, and detailed methodology • The characteristics of the included studies were provided • Comprehensive search of the literature • Data extraction was done in duplicate • The quality of the included studies was assessed and documented • Publication bias was assessed and reported (funnel plot)	• One author performed the initial screen of the literature

NMA = network meta-analysis

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
King, 2016[2]	
• Abstinence at 10 wks, range: 14.8% to 28% (patch; 2 RCTs), 23% (bupropion, 1 RCT), 13.1% to 28% (placebo, 3 RCTs) • No statistically significant increase in abstinence rates for NRT interventions compared with controls for all outcomes (including abstinence or reduction in CPD at 4 wks, abstinence at 12 wks; 1 RCT per outcome) • Compliance and safety variably reported • Compliance ranged from 29% to 85%, though this includes the open-label trials • No safety issues reported	• The effectiveness of NRT is unclear due to insufficient study sample sizes • Strategies aimed at increasing study compliance and retention in an adolescent population, such as qualitative analyses of NRT acceptance, may be helpful
Schwartz, 2016[8]	
• 12 weeks: 7-day PP of SLT abstinence was significantly higher in the varenicline group (176/370, 48%) vs. the placebo group (124/374, 33%) (RR = 1.45, (95% CI, 1.22 to 1.72; $p < 0.0001$; $I^2 = 0\%$)) (RD = 13%, (95% CI = 4% to 23%; $p = 0.008$)) • 12 weeks: the NNT was 8 • 26 weeks: 7-day PP of SLT abstinence was not significantly higher in the varenicline group (124/251, 49%) vs. the placebo group (99/256, 39%) (RR = 1.38, (95% CI, 0.93 to 2.03; $p = 0.11$; $I^2 = 51\%$)) (RD = 14%, (95% CI, -3% to 32%; $p = 0.10$)) • Incidence of nausea was not significantly higher in the varenicline group (83/370, 22.4%) vs. the placebo group (19/374, 5.1%) (RR = 2.46, (95% CI, 0.20 to 30.43; $p = 0.48$; $I^2 = 77\%$)) • Incidence of sleep disturbance was not significantly higher in the varenicline group (74/370, 20%) vs. the placebo group (42/374, 11.2%) (RR = 1.60, (95% CI, 0.79 to 3.25; $p = 0.19$; $I^2 = 61\%$)) • Incidence of mood disorders was not significantly lower in the varenicline group (6/370, 1.6%) vs. the placebo group (9/374, 2.4%) (RR = 0.71, (95% CI, 0.26 to 1.90; $p = 0.49$; $I^2 = 0\%$))	• "This meta-analysis shows that varenicline therapy is associated with significantly higher 7-day point prevalence of SLT abstinence at 12 weeks but not at 26 weeks in SLT users." *Page 13* • "The most commonly reported adverse effects of varenicline were nausea, sleep disturbance, and mood disorders. While nausea and sleep disturbance occurred at nonsignificantly higher rates in the varenicline arm compared to the placebo arm, mood disorders occurred at a nonsignificantly lower rate." *Page 13* • "Since the participants in all three trials included in our meta-analysis received some form of behavioral therapy, we cannot separate the independent effectiveness of counseling on patient adherence to varenicline nor can we determine the effectiveness of varenicline without counseling." *Page 14*
Ebbert, 2015[9]	
<u>Bupropion vs. Placebo</u> • 6 months or greater abstinence: bupropion (25/147) vs. placebo (28/146) (RR = 0.89, (95% CI, 0.54 to 1.44; $I^2 = 0\%$))	• "Varenicline appears to increase tobacco abstinence rates among Swedish snus and American ST users and could be offered clinically. The nicotine lozenge also increases ST abstinence rates though confidence in this

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
NRT vs. Placebo • 6 months or greater abstinence: nicotine patch (156/540) vs. placebo (138/543) (RR = 1.13, (95% CI, 0.93 to 1.37; I^2 = 14%)) • 6 months or greater abstinence: nicotine gum (41/156) vs. placebo (41/154) (RR = 0.99, (95% CI, 0.68 to 1.43; I^2 = 0%)) • 6 months or greater abstinence: nicotine lozenge (274/768) vs. placebo (199/761) (RR = 1.36, (95% CI, 1.17 to 1.59; I^2 = 0%)) • 6 months or greater abstinence: all NRT (471/1464) vs. placebo (378/1458) (RR = 1.24, (95% CI, 1.11 to 1.39; I^2 = 48%)) Varenicline vs. Placebo • 6 months abstinence: varenicline (112/251) vs. placebo (85/256) (RR = 1.34, (95% CI, 1.08 to 1.68; I^2 = 0%))	effect is limited due to the absence of placebo controls. The efficacy of varenicline and the nicotine lozenge are lower than observed with these medications among cigarette smokers attempting to quit smoking (Stead 2012; Cahill 2013). Evidence for the effect of bupropion SR for the treatment of ST use is inconclusive." *Page 11*
Hughes, 2014[3]	

Bupropion vs. Placebo
• Bupropion vs. placebo – 44 studies, n = 13,728
• 6 month or greater abstinence: bupropion (1507/7646) vs. placebo (701/6082) (RR = 1.62, (95% CI, 1.49 to 1.76; I^2 = 0%))
• 12 month (27 studies): bupropion vs. placebo (RR = 1.59, (95% CI, 1.44 to 1.76)
• Placebo quit rates ranged from 0% to 33%; bupropion group quit rates ranged from 4% to 43%
 	
Bupropion vs. NRT
• Bupropion vs. NRT – 8 studies (RR = 0.96, (95% CI, 0.85 to 1.09; I^2 = 27%)
• No single NRT (patch, lozenge, choice of NRT) showed a significant difference compared to bupropion
  ○ Patch versus bupropion: 6 studies (n = 1634), RR = 1.04 (95% CI, 0.84 to 1.27)
  ○ Lozenge versus bupropion: 2 studies (n = 694), RR = 0.91 (95% CI, 0.67 to 1.22)
  ○ Patch plus lozenge: 2 studies (n = 720), RR = 0.74 (95% CI, 0.55 to 0.98)
  ○ Choice of NRT: 2 studies (n = 1038), RR = 1.08 (95% CI, 0.87 to 1.33)
 	
Adverse Events
• Common side effects bupropion: insomnia (30% to 40% of patients), dry mouth (10%), nausea (NR), allergic reactions at a rate of about 1 to 3 per 1000 (e.g., pruritus, hives, angioedema and dyspnea), hypersensitivity at
	• "The existing evidence supports a role for bupropion and nortriptyline in clinical practice. Nicotine replacement therapy has proven efficacy in over 100 studies (Stead 2012) and has a very benign side-effect profile. There is insufficient published evidence to conclude either bupropion or nortriptyline has superior efficacy to NRT or vice versa." *Page 26*
	• "All smoking cessation medications can produce clinically significant adverse effects. When people are initially screened for potential adverse effects, however, fewer than 10% of those on antidepressants for smoking cessation stop taking the medications due to adverse effects. Although bupropion use has been associated with deaths in lay public reports, currently there is insufficient evidence to state that bupropion caused these deaths. There has also been concern about antidepressants such as bupropion being associated with psychiatric disorders including suicidal ideation and suicide attempts. Again, it is not clear that there is a causal relationship." *Page 26*

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
a rate of less than 1 per 1000 • SAEs for bupropion versus control (not certain if placebo in all cases) RR = 1.30, (95% CI, 1.00 to 1.69) • Psychiatric SAEs no difference in bupropion versus placebo (RR = 0.60 (95% CI, 0.28 to 1.28) • CV events bupropion versus placebo: RR = 1.16 (95% CI, 0.65 to 2.06) • No significant differences of serious AEs for bupropion versus placebo/control groups, and the rates were small for each (range 0.4% to 2.1%)	
Mills, 2014[14]	
Random-Effects MA for CV Events *# of RCTs* | *Comparison* | *Events* | *RR (95% CI)* | *I^2 (%)* 21 | NRT vs. pl | 202/6329 vs. 82/5318 | 1.81 (1.35-2.43) | 0 27 | Bup vs. pl | 50/5947 vs. 83/4455 | 1.03 (0.71-1.50) | 0 18 | Var vs. pl | 63/5469 vs. 41/3603 | 1.24 (0.85-1.81) | 0 3 | Bup vs.NRT | 4/367 vs. 2/366 | 1.40 (0.25-7.82) | 2 1 | Var vs.NRT | 0/378 vs. 2/379 | 0.20 (0.01-4.16) |
Random-Effects MA for MACE Events *# of RCTs* | *Comparison* | *Events* | *RR (95% CI)* | *I^2 (%)* 21 | NRT vs. pl | 12/6329 vs. 7/5318 | 1.38 (0.58-3.26) | 0 27 | Bup vs. pl | 15/5947 vs. 25/4455 | 0.57 (0.31-1.04) | 0 18 | Var vs. pl | 22/5469 vs. 13/3603 | 1.44 (0.73-2.83) | 0 3 | Bup vs.NRT | 0/367 vs. 1/366 | 0.34 (0.01-7.94) | 1 | Var vs.NRT | 0/378 vs. 2/379 | 0.20 (0.01-4.16) |
	• "Smoking cessation therapies do not appear to raise the risk of serious cardiovascular disease events." *Page 1* • "We found no increase in the risk of all cardiovascular disease events with bupropion (relative risk [RR], 0.98; 95% confidence interval [CI], 0.54–1.73) or varenicline (RR, 1.30; 95% CI, 0.79–2.23). There was an elevated risk associated with nicotine replacement therapy that was driven predominantly by less serious events (RR, 2.29; 95% CI, 1.39–3.82). When we examined major adverse cardiovascular events, we found a protective effect with bupropion (RR, 0.45; 95% CI, 0.21–0.85) and no clear evidence of harm with varenicline (RR, 1.34; 95% CI, 0.66–2.66) or nicotine replacement therapy (RR, 1.95; 95% CI, 0.26–4.30)." *Page 1*

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Random-Effects NMA for CV and MACE *Comparison* | *All CV (RR, 95% CI)* | *MACE (RR, 95% CI)* NRT vs. pl | 2.29 (1.39–3.82) | 2.29 (1.39–3.82) Bup vs. pl | 0.98 (0.54–1.73) | 0.98 (0.54–1.73) Var vs. pl | 1.30 (0.79–2.23) | 1.30 (0.79–2.23) Bup vs.NRT | 0.43 (0.19–0.91) | 0.43 (0.19–0.91) Var vs.NRT | 0.56 (0.25–1.27) | 0.56 (0.25–1.27)	
Hajek, 2013[10]	
<u>Bupropion vs. Placebo</u> • 12 month or greater abstinence (6 studies): bupropion (238/852) vs. placebo (205/845) (RR = 1.15, (95% CI, 0.98 to 1.35; I^2 = 0%) <u>NRT vs. Placebo</u> • 12 month or greater abstinence (1 study): NRT gum (19/72) vs. placebo (13/71) (RR = 1.44, (95% CI, 0.77 to 2.69)) • 12 month or greater abstinence (1 study): NRT inhaler (17/81) vs. placebo (19/87) (RR = 0.96, (95% CI, 0.54 to 1.72)) <u>Varenicline vs. Placebo</u> • Significant benefit of extended varenicline (single study, n = 1210) (RR 1.18, 95% CI 1.03 to 1.36)	• "Extended treatment with varenicline may prevent relapse. Extended treatment with bupropion is unlikely to have a clinically important effect. Studies of extended treatment with nicotine replacement are needed." *Page 2*
Stanton, 2013[11]	

<u>Adverse Eventss</u>
• 4% of patients reported AEs, and eight patients dropped out of the trial due to AEs
• 2 serious AEs (1 intentional overdose with study medication and other substances; 1 ingestion of other toxic substance)
 	
<u>Bupropion vs. Placebo</u>
• No significant benefit of standard dose bupropion versus placebo (RR = 1.49 (95% CI, 0.55 to 4.02)) or lower 150 mg dose (RR= 0.33 (95% CI, 0.07 to 1.58))
 	
<u>NRT vs. Placebo</u>
• NRT patches and gum vs. placebo at 6 months: not significant
  ○ RR = 4.12 (95% CI, 0.92 to 18.52) for patches vs. placebo
  ○ RR = 1.74 (95% CI, 0.34 to 9.00) for gum vs. placebo
	• "There were few trials with evidence about pharmacological interventions (nicotine replacement and bupropion), and none demonstrated effectiveness for adolescent smokers. There is not yet sufficient evidence to recommend widespread implementation of any one model. There continues to be a need for well-designed adequately powered randomized controlled trials of interventions for this population of smokers." *Page 2*

Table A3: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td colspan="2">Cahill, 2012[4]</td></tr>
<tr><td>
<u>Varenilcine vs. Placebo</u>
• 13/15 trials found varenicline significantly more effective than placebo at all time points
• 6 month abstinence for standard-dose varenicline vs. placebo: RR = 2.27 (95% CI, 2.02 to 2.55)
• 6 month abstinence for variable or lower dose varenicline versus placebo: RR = 2.09 (95% CI, 1.56 to 2.78)

<u>Varenicline vs. NRT</u>
• For 1 trial of varenicline vs. NRT patch, abstinence at 24 weeks: RR = 1.13 (95% CI, 0.94 to 1.35)s
• For 1 trial of varenicline vs. NRT patch, abstinence at 52 weeks: RR = 1.29 (95% CI, 0.99 to 1.67

<u>Adverse Events: Varenicline vs. Placebo</u>
• MA for main AEs for varenicline versus placebo:
  ○ Nausea: RR = 3.28 (95% CI, 2.89 to 3.73)
  ○ Insomnia: RR = 1.62 (95% CI, 1.40 to 1.88)
  ○ Abnormal dreams: RR = 2.91 (95% CI, 2.34 to 3.62)
  ○ Headache: RR = 1.18 (95% CI, 1.03 to 1.36)s
</td><td>
• "The evidence from the trials conducted so far indicates that varenicline increases the chances of successful smoking cessation, between two- and three-fold compared with placebo (RR 2.27, 95% CI 2.02 to 2.55). This estimate has remained stable, despite the growing inclusion of pragmatic trials in real-world settings and in particular groups of smokers normally excluded from clinical trials, e.g. in lower- and middle-income countries, and in disease specific populations." *Page 11*
</td></tr>
<tr><td colspan="2">Mills, 2012[12]</td></tr>
<tr><td>
• Random-effects MTC results for relevant comparisons:
<table>
<tr><th></th><th colspan="4">Smoking abstinence, RR (95% CrI)</th></tr>
<tr><th></th><th>Short-term</th><th>3 m</th><th>6 m</th><th>12 m</th></tr>
<tr><td>Standard dose patch vs. bupropion</td><td>1.12 (1.02 – 1.22)</td><td>0.96 (0.84 – 1.10)</td><td>0.99 (0.86 – 1.14)</td><td>0.94 (0.77 – 1.15)</td></tr>
<tr><td>Standard dose patch vs. varenicline</td><td>1.43 (1.26 – 1.60)</td><td>1.48 (1.23 – 1.75)</td><td>1.38 (1.15 – 1.64)</td><td>1.65 (1.29 – 2.07)</td></tr>
<tr><td>High-dose patch vs. bupropion</td><td>0.98 (0.88 – 1.09)</td><td>0.87 (0.66 – 1.13)</td><td>0.73 (0.58 – 0.91)</td><td>0.81 (0.60 – 1.09)</td></tr>
<tr><td>High-dose patch vs. varenicline</td><td>1.29 (1.12 – 1.46)</td><td>1.40 (1.05 – 1.80)</td><td>1.05 (0.80 – 1.36)</td><td>1.47 (1.06 – 2.01)</td></tr>
</table>
• Bupropion was more effective than standard-dose NRT patch at 4 weeks, and was not significantly more effective than any other intervention otherwise
</td><td>
• "In conclusion, although most pharmacotherapies provide significantly improved cessation over inert controls over the short and longer term in the pairwise analyses, our MTC demonstrates that varenicline is significantly more effective than other active pharmacotherapy interventions at most time points including at the long-term follow-up. In light of the current economic climate and the drive towards efficiency savings in health services across the world, policy-makers and clinicians should consider the relative costs of the different treatment options when making decisions about selection of appropriate treatments. While considering that not all smokers tolerate medications and that a variety of treatment options should remain available, our data may be used to help guide the development of guidelines and policies to promote the selection of the most efficacious first-line medications for smoking cessation." *Page 596*
</td></tr>
</table>

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
• Varenicline had significantly greater smoking abstinence rates than all other interventions, except for the comparison with high-dose NRT patch or combination NRT at 6 months • Varenicline had the highest probability of being the best treatment at all time points (short-term, three months, six months, and 12 months)	
Stead, 2012[13]	

<u>NRT vs. Placebo</u>
• RR of abstinence for any form of NRT relative vs. placebo/no NRT was 1.60 (95% CI 1.53 to 1.68); GRADE assessment: high quality
• Pooled RRs for abstinence by NRT type vs. placebo/no NRT:
  ○ gum: 1.49 (95% CI 1.40 to 1.60, 55 trials)
  ○ patch: 1.64 (95% CI 1.52 to 1.78, 43 trials)
  ○ oral tablets/lozenges 1.95 (95% CI 1.61 to 2.36, 6 trials)
  ○ inhaler: 1.90 (95% CI 1.36 to 2.67, 4 trials)
  ○ nasal spray: 2.02 (95% CI 1.49 to 2.73, 4 trials)
  ○ oral spray: 2.48 (95% CI 1.24 to 4.94, 1 trial)
 	
<u>NRT vs. Bupropion</u>
• No evidence of a difference in efficacy between NRT and bupropion (RR for abstinence: 1.01; 95% CI 0.87 to 1.18, 5 trials)
  • "Adverse effects from using NRT are related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and tablets. There is no evidence that NRT increases the risk of heart attacks." *Page 2*
 	
<u>Adverse Events</u>
• odds of CV for patients on NRT compared to placebo (OR = 1.88, (95%CI, 1.37 to 2.57))
	• "All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50 to 70%, regardless of setting. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT." *Page 2*

AE = adverse event; Bup = bupropion; CI = confidence interval; CPD = cigarettes per day; CrI = credible interval; CV = cardiovascular; m = months; MA = meta-analysis; MACE = major adverse cardiovascular event; NRT = nicotine replacement therapy; pl = placebo; RCT = randomized controlled trial; RR = risk ratio; SAE = serious adverse events; var = varenicline; wks = weeks

APPENDIX 5: Additional References of Potential Interest

Previous Versions of Included Systematic Reviews

Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2011;(2).

Ebbert J, Montori VM, Erwin PJ, Stead LF. Interventions for smokeless tobacco use cessation. Cochrane Database Syst Rev. 2011;(2).

Systematic Reviews Excluded due to Overlap with Included Systematic Reviews

McKee SA, Smith PH, Kaufman M, Mazure CM, Weinberger AH. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. Nicotine Tob Res. 2015 Oct 6.

Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. BMJ. 2012;344:e2856.

Leung LK, Patafio FM, Rosser WW. Gastrointestinal adverse effects of varenicline at maintenance dose: a meta-analysis. BMC Clin Pharml. 2011;11:15.

Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ. 2011 Sep 6;183(12):1359-66.