Cardiovascular Events Associated with Smoking Cessation Pharmacotherapies: A Network Meta-Analysis

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Cardiovascular Events Associated with Smoking Cessation Pharmacotherapies: A Network Meta-Analysis

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Abstract

***Background*—**Stopping smoking is associated with many important improvements in health and quality of life. Use of cessation medications is recommended to increase the likelihood of quitting. However, there is historical and renewed concern that smoking cessation therapies may increase the risk of cardiovascular disease (CVD) events associated within the quitting period. We aimed to examine whether the three licensed smoking cessation therapies: nicotine replacement therapy (NRT); bupropion, and; varenicline and were associated with an increased risk of CVD events using a network meta-analysis.

***Methods and Results*—**We searched ten electronic databases, and made communication with authors of published randomized clinical trials (RCT), and accessed internal US Food and Drug Administration (FDA) reports. We included any RCT of the 3 treatments that reported on CVD outcomes. Among 63 eligible RCTs involving 21 NRT RCTs, 28 bupropion RCTs and 18 varenicline RCTs, we found no increase in the risk of all-CVD events with bupropion (RR 0.98, 95% Confidence Intervals [CIs], 0.54-1.73) or varenicline (RR 1.30, 95% CI, 0.79-2.23). There was an elevated risk associated with NRT that was predominantly driven by less serious events (2.29, 95% CI, 1.39-3.82). When we examined major adverse cardiovascular events (MACE) 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 NRT (RR 1.95, 95% CI, 0.26-4.30).

***Conclusions*—**Smoking cessation therapies do not appear to raise the risk of serious CVD events.

Key words: meta-analysis, statistical analysis, smoking, Smoking cessation, Bayesian, Meta-analysis, Pharmacotherapies, Randomized trials

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Introduction

Smoking is the leading preventable cause of death around the world.[1] Approximately 50% of long-term smokers will die a smoking-related death.[2] Early cessation of smoking is associated with important increases in life expectancy, improved quality of life and reduced health care costs for smoking associated conditions.[2] Chief among the benefits of smoking cessation are improved cardiovascular health.[3, 4] For these reasons, clinical practice guidelines in the US recommend the use of smoking cessation pharmacotherapies with all adult smokers interested in quitting unless contraindicated.[5, 6]

In North America, there are three approved first-line classes of therapies: nicotine replacement therapy (NRT); bupropion, an antidepressant, and; varenicline, a nicotine receptor partial agonist. Many randomized clinical trials and systematic reviews have demonstrated these agents as effective for promoting smoking cessation.[7, 8] The medications have different mechanisms of action and side effect profiles. All have undergone some scrutiny for potential cardiovascular effects when coming onto to market. When NRT first came onto the market, there were concerns in the literature and popular press about its safety profile with regard to cardiovascular events, particularly among users who continued to smoke.[9] Clinical trials and laboratory research that followed indicated NRT was safe even with high dose patch, combination NRT, and concurrent smoking.[10-12] With bupropion, three trials consisting of 792 total smokers with cardiovascular disease (CVD) reported greater cardiovascular events among participants assigned to active versus placebo drug; the differences were not statistically significant, however, the trials were not powered for safety.[13-15] Similar concerns have been raised about varenicline. In 2011, a meta-analysis by Singh et al. involving 8216 participants reported that varenicline use may be associated with increased minor and major cardiovascular

events (odds ratio [OR] 1.72, 95% confidence intervals [CIs], 1.09-2.71), a finding at odds with the goal of smoking cessation that garnered a great deal of media attention.[16] A follow-up meta-analysis found the difference between varenicline and placebo to be statistically and clinically nonsignificant.[17]

Recognizing the large number of smokers attempting to quit by using pharmacotherapies, and the widespread media reports of cardiovascular risks associated with pharmacotherapies, making clear public health messages remains a priority. At the request of the FDA, the drug maker (Pfizer Inc) recently conducted a meta-analysis based on major adverse cardiovascular events (MACE), that were defined as cardiovascular death, nonfatal MI, and nonfatal stroke.[18] Using individual patient data from industry sponsored randomized clinical trials (RCTs), the Hazard ratio [HR] was not significant (HR=1.95, 95% CI 0.79, 4.82). The most recent FDA safety communication on varenicline from December 2012 indicates the events were uncommon both in active and placebo drug conditions and the increased risk was not statistically significant. Similarly, an FDA mini-sentinel evaluation evaluating CVD events among 89,519 varenicline users and 113,378 bupropion users found no difference in CVD event risk between varenicline and bupropion (incidence rate ratio 1.02, 95% CI, 0.71-1.47).[19]

The concern about varenicline has led investigators to more closely examine the other pharmacotherapies. A large cohort study found no difference in CVD events between varenicline and bupropion among a nationwide study in Denmark (HR, 0.96, 95% CI, 0.67 to 1.39).[20] A meta-analysis examining only NRT found an increased risk for less serious cardiovascular events, such as tachycardia and non-specific chest pain, but did not examine MACE.[21] Notably, few of the RCTs have been conducted within populations with secondary CVD risk profiles.[15, 22] Most trials have compared an active medication to a placebo, with few trials evaluating head-to-

head comparisons of cessation medications. Using a statistical technique called network meta-analysis we can examine both direct (head-to-head RCTs) and indirect evidence and thus increase the power and interpretability of a comparative analysis.[23] We aimed to examine the comparative safety of NRT, bupropion and varenicline, evaluating both all-CVD events and MACE reported in published RCTs and FDA reports in smokers with and without pre-existing CVD.[23]

Methods

Eligibility Criteria

We included any randomized clinical trial (RCT) of: NRT at any marketed dose or combination; bupropion at licensed doses, or; varenicline at licensed doses. Studies had to enroll smokers at initiation of therapy and report on whether or not any CVD events occurred. We included studies of any duration as long as they reported on a complete trial, defined as having provided the preplanned duration of study drug. For varenicline RCTs, we obtained the individual level data via a request about the confidential FDA report.[18]

Study endpoints

We considered two definitions of cardiovascular events: 1) all-cardiovascular events, defined as clinical diagnoses of any cardiovascular event considered in previous systematic reviews on risk of cardiovascular events associated with smoking cessation therapies;[16, 17, 24] and 2) major adverse cardiovascular events (MACE) using the same criteria as the FDA report.[18] These included cardiovascular death, non-fatal MI, and non-fatal stroke. In circumstances where an event is reported but not attributed to a group, we contacted the study authors for clarification.

Search strategy

In consultation with a medical librarian, we established a previously published search strategy

(available in appendix).[24] We searched independently, in duplicate, the following 10 databases (from inception to March 20, 2013): MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science, and databases including the full text of journals (*OVID, ScienceDirect*, and *Ingenta*, which includes articles in full text from 1993). In addition, we searched the bibliographies of published systematic reviews and health technology assessments and contacted the authors of individual RCTs. Searches were not limited by language, sex or age.

Study selection

Two investigators (PW, SE) independently and in duplicate scanned abstracts and then obtained the full text reports of RCTs evaluating the interventions of interest. After obtaining full reports of the candidate trials the same reviewers independently assessed eligibility from full text papers.

Data collection

Two reviewers (PW, SE) conducted data extraction independently using a standardized pre-piloted form with the categories of CVD, available from the authors upon request. Reviewers collected information about the smoking intervention, the population studied (age, sex, underlying conditions), treatment dosages and dosing schedules, CVD events and loss to follow up. Study evaluation included general methodological quality features using a modified Cochrane risk of bias tool.[25]

Data analysis

We assessed inter-rater reliability on inclusion of articles using the *Phi* statistic, which provides a measure of inter-observer agreement independent of chance.[26] Our analysis required two approaches: first pair-wise meta-analysis of all direct RCT evidence, and secondly, a network

meta-analysis that includes both the direct RCT evidence, and indirect comparisons of those treatments. We evaluated the major outcomes as all-CVD events and MACE. For pair-wise meta-analysis we used the conventional DerSimonain-Laird approach to account for unexplained heterogeneity between studies.[27] We calculated the Relative Risk [RR] and 95% Confidence Intervals [CIs] of outcomes according to the number of events reported in the original studies or sub-studies. We calculated the I^2 statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity. We considered an I^2 value greater than 30% to be important and investigated the cause of heterogeneity using sub-group analysis and random effects meta-regression.

In the absence of many head-to-head trials evaluating all interventions, we conducted a Bayesian random-effects network meta-analysis.[28,29] A detailed description of the underlying statistical model is provided in the appendix.

Results

Study Characteristics

Figure 1 displays the flow-diagram documenting the search and inclusion of relevant studies. **Supplemental table 1** lists the excluded studies, as they did not report on CVD events. Our review identified 63 eligible RCTs[10, 13-15, 22, 30-87] that reported on cardiovascular events involving 30,508 patients. **Table 1** displays the study characteristics. Out of these 63 trials, there were 58 two-armed trials, 3 three-armed trials and 2 four-armed trials. For trials that had multiple arms due to dosage differences, we pooled those arms for each treatment. 19 RCTs evaluated NRT versus placebo[10, 30-34, 36-38, 40-46, 49, 53, 68]; 27 RCTs evaluated bupropion versus placebo[13-15, 47-49, 51-71]; 18 RCTs evaluated varenicline versus placebo[22, 54, 55, 72-79, 81-87]; 1 RCT evaluated high-dose

NRT versus placebo[39], 1 RCT evaluated combination NRT versus control[35], 2 RCTs evaluated bupropion versus varenicline[54, 55], 3 RCTs evaluated bupropion versus NRT,[49, 53, 68] and; 1 RCT evaluated varenicline versus NRT.[80] Study quality was variable (**Supplemental table 2**).

The 63 RCTs collectively included 30,508 participants. Among RCTs examining specific CVD risk groups, eight trials included patients with cardiovascular disease,[10, 13, 15, 22, 46, 47, 61, 87] four trials included patients with chronic obstructive pulmonary disease (COPD),[53, 59, 64, 77] and one trial included perioperative patients.[74] These RCTs were included in our analysis that was restricted to high-risk patients. The median duration of treatment across treatments was 12 weeks (IQR = 8-12 weeks) while the median duration of follow-up trial time was 12 months (IQR = 6-12 months). Attrition across the period of the trials was not importantly different by intervention or controls (NRT vs placebo 23% vs 20%; bupropion vs placebo 26% vs 31%; varenicline vs placebo 28% vs 29%).

Pairwise comparisons

We examined pairwise comparisons of all interventions with available head-to-head data. The results are reported in **Table 2**. We found no major evidence of heterogeneity as I^2 values were equal or close to 0% at all times.

For NRT, the risk of any CVD event was statistically significantly increased compared with placebo (RR 1.81, 95% CrI, 1.35-2.43). When this was restricted to only MACE, confidence intervals became wide and thus, did not suggest statistical evidence of harm (RR, 1.38, 95% CrI, 0.58-3.26). When this was restricted to high-risk patients, the relative decreased and confidence intervals became wider.

For buproprion, the results suggested a direction of effect that is protective against MACE for the entire study population (RR 0.57, 95% CrI, 0.31-1.04). When the population was

restricted to high-risk patients, the trend remained, but confidence intervals became slightly wider. When looking only at MACE the relative risk became closely identical to 1.00.

For varenicline, the relative risk was slightly larger than 1.00 (i.e., no difference) for both outcome definitions and population groups, but confidence intervals were wide in all instances.

Network Meta-analysis

Figure 2 displays the trial network. The network meta-analysis results are reported in **table 3**. The findings are similar to the pairwise findings and demonstrate that NRT was significantly associated with increased risk of all-CVD events. In particular, risk of events with NRT was statistically increased versus placebo and bupropion. However, when restricted to only MACE category of events, NRT was no longer significantly associated with harm.

Bupropion appears to protect for the risk of MACE relative to both NRT and varenicline. Varenicline was not associated with either benefit or harm in the network meta-analysis, but had a significantly higher risk of harm compared with bupropion (**Table 2**).

High-risk populations

When we examined only RCTs that enrolled high-risk populations, the direction of effect was similar to the complete trials analysis, but none of the comparisons reached statistical significance (**Table 2**).

Sensitivity analysis

We removed the MACE events from the NRT analysis to examine what endpoints were driving the harmful effect of NRT. When we removed all MACE events, the RR of NRT was 1.89 (95% CrI, 1.31-2.73). The most commonly reported NRT adverse events were heart palpitations. When we included only events we considered to be well-known lower severity adverse events associated with NRT (ie. palpitations, bradycardia, and arrhythmia), the pooled RR was 2.08

(95% CrI, 1.35-3.19).

We also removed studies with shorter than 12 months duration to investigate potential effect-modification by study duration. This analysis yielded highly similar results to the main analysis for buproprion versus placebo, RR=0.97 (95% CrI, 0.56-1.59), and for varenicline versus placebo RR=1.45 (95% CrI, 0.86-2.62). However, for NRT the increased risk of all CVD was more pronounced and statistically evident RR=3.03 (95% CrI 2.04-4.67). Further, varenicline was significantly less likely than NRT to cause CVDs, RR=0.48 (95%CrI, 0.24-0.96).

Discussion

Our study addressed whether smoking cessation therapies increase the risk of CVD events using two definitions, one addressing all-CVD events that included more minor events, such as tachycardia, and one that followed FDA definitions of MACE.[18]

Our study demonstrates that all three evaluated therapies were not harmful for MACE events. Bupropion appears to have a protective effect, whereas varenicline, was not significantly associated with harm. NRT, the most widely used pharmacotherapy for smoking cessation was associated with an increase in CVD events that was driven by lower risk events, typically tachycardia, a well-known and largely benign effect of NRT.[21] When our analysis was restricted to individuals with a higher risk-profile of having an event, because of previous history of predisposing conditions, we did not find evidence of increased risk with any pharmacotherapy, although this was based on a smaller sample.

There are several strengths and limitations to consider in this study. Strengths include the comparative safety evaluation across pharmacotherapies, a strategy that, to our knowledge, has not been applied previously. We evaluated two important definitions of CVD events, both all-

CVD events, and the FDA definition of MACE, considered to be a more stringent definition of patient important outcomes.[18] Because we applied two different categories of events, our findings can inform where previous evaluations of safety may have been limited. Limitations of our review are predominantly driven by the necessity that trial reports or the FDA report provided information on the outcomes of interest. Because concern about CVD risk with smoking cessation is a relatively new issue, many trials that reported on effectiveness outcomes did not report on CVD safety outcomes.[24] Efforts to reduce this potential reporting bias by contacting study authors were hampered by non-response and the long period of time since the trials were published, particularly for NRT trials. Given the heterogeneous reporting of CVD events in RCTs, we used a composite outcome of MACE events, as used by the FDA.[18] It is possible that individual components of the composite would find differing effects, but we acknowledge that any analysis of these would be hampered by lower power to detect a signal of harm. We found low rates of MACE events across the three interventions resulting in wide credible intervals. It is possible that with a vastly larger dataset, treatment outcomes would change.[18] However, we conducted post-hoc power calculations to estimate the power of our comparisons for MACE and found acceptable levels of power for all comparisons (see appendix 3). Our varenicline analysis was hampered by lower power. Appendix For the most part, the findings are largely limited to smokers without pre-existing heart disease. We found similar rates of attrition across interventions, these ranged from 20-29%, yet it is possible that attrition reflects intolerability of the intervention and thus misses some events. We did not report the Bayesian probability of risk because these are not widely understood and because the probability ranking can vary widely depending on the sparseness of the data.[88] Throughout this analysis, we present the point estimates with credible intervals. Although some analyses did not reach statistical

significance, the possibility of risk still exists when credible intervals include an estimate that would be considered clinically important.

Our study found statistically significant evidence of all-CVD events associated with NRT use. However, when we restricted this to MACE events, the finding was no longer statistically significant. When we examined these findings in a sensitivity analysis, we found that the treatment effects were predominantly driven by lower level CVD events (RR 1.91), including tachycardia and arrhythmia, both well-known adverse events of NRT use,[9, 21, 89, 90] and occurred primarily in studies with longer periods of follow-up.

There are several possible explanations why NRT use may increase some CVD events and this has been recognized for some time, although it is not well understood, nor a major clinical concern.[9, 21, 89, 90] Chiefly, many smokers have a long history of smoking that may have established coronary artery disease. Those patients with unstable coronary syndrome, may be exhibiting coronary vasoconstriction associated with plaque ruptures due to increased strain of quitting and palpitations associated with NRT.[89] Second, for those patients receiving NRT and continuing to smoke, high nicotine serum concentrations may stimulate the sympathetic nervous system response, thereby increasing blood pressure, stroke volume, and heart output.[89] Yet, importantly, some research has documented more CVD events among patients with heart disease who smoked on a placebo than on a nicotine patch.[10] Further, equivalent proportions of palpitations or chest pain were found among those who smoked or did not smoke during nicotine patch therapy.[91]

Only a few years on market, electronic cigarettes or e-cigarettes are a relatively new, and unregulated, approach to nicotine delivery. Consequently, the safety of these products and their use for quitting cigarette smoking has not been well evaluated. At this time, they are not

considered cessation devices, and their contents and risk profiles are just beginning to be explored.[92, 93] Different guidelines and algorithms exist on the choice of cessation pharmacotherapy according to patient history of smoking, substance abuse, and chronic disease risk profiles. For example, both the Mayo Clinic and the Ottawa model for smoking cessation recommend the use of NRT among at-risk CVD patients,[94] while the US Surgeon General report (2010) advocates avoidance of NRT for two weeks post major CVD event.[95] Given the current findings of low risk of serious CVD events attributed to smoking cessation pharmacotherapies, combined with the well-established CVD and mortality risks of continued smoking, the benefits of use would seem to outweigh the risks; however, further study is needed, particularly investigation of the use of cessation medications with smokers hospitalized for ST-elevation myocardial infarction.[95]

Our findings should be placed in the context of other available evidence. The concern about smoking cessation therapies increasing risk of CVD events was most widely reported by Singh et al in 2011 in an evaluation of varenicline versus placebo RCTs. [16] Using data from 14 RCTs, the study authors reported a Peto odds ratio for all-CVD events of 1.72 (95% CI, 1.09-2.71). The Peto odds ratio is an artifact of a fixed effects analysis and therefore has tighter confidence intervals than random-effects models.[96] Applying a random-effects analysis to their dataset yields a RR of 1.43 (95% CI, 0.91-2.25), which is not very different from the findings in our analysis of 16 RCTs (RR 1.24, 95% CI, 0.85-1.81). Much has been written about the choice of effect measure for RCTs and it is well understood that odds ratios can be perceived as inflating the treatment effects.[97] Prochaska has demonstrated this with the varenicline and CVD risk data.[17, 98] As a result of the controversy about varenicline and CVD risk, the FDA conducted their own meta-analysis using individual patient data addressing their definition of MACE on 30-

day post-treatment outcomes and found a hazard ratio of 1.95 (95% CI, 0.79, 4.82), which is not very different from the findings of our analysis based on additional aggregate data (RR 1.57, 95% CI, 0.67-3.17). Our findings that less clinically concerning events drove the significant finding of NRT for all-CVD events is consistent with findings from a meta-analysis we previously published based on RCTs and observational data on the outcome of chest pain and palpitations (RR 1.66, 95% CI, 1.22-2.28).[21] While the comparative effects of each therapy is, to our knowledge, a new approach to evaluating safety of smoking cessation therapies, a recent nation-wide observational study in Denmark examined the comparative harms of bupropion and varenicline and did not demonstrate significant harm from either treatment.[20] Similar findings were reported in the US.[19]

The potential cardio-protective role of bupropion is not well understood. We did not find bupropion protective against all-CVD events, however, we did find a statistically significant protective effect for MACE. It is possible that the antidepressant origins of bupropion anti-depressant origins reduce vascular stress.[99, 100] However, at higher doses also has sympathomimetic activity and can increase heart rate and blood pressure.[99, 100] Based on our current findings, bupropion may be cardio-protective, likely through its effects on increasing smoking cessation and alleviating depression, though closer investigation of bupropion's cardiovascular effects are warranted.

Physicians often weigh the benefits and risks of available treatments including cessation pharmacotherapies. Concerns about adverse events need to be balanced with the consistent evidence for the benefit of smoking cessation and patients should be counseled about what adverse events may be associated with smoking cessation therapies, the symptoms associated with the withdrawal period from cigarettes, and symptoms that may be due to existing diseases.

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References:

1. Peto R, Lopez AD, Boreham J, Thun M, Heath C, Jr., Doll R. Mortality from smoking worldwide. *Br Med Bull.* 1996;52:12-21.

2. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med.* 2013;368:341-350.

3. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Arch Intern Med.* 2000;160:939-944.

4. Glantz S, Gonzalez M. Effective tobacco control is key to rapid progress in reduction of non-communicable diseases. *Lancet.* 2012;379:1269-1271.

5. The Health Consequences of Smoking: A Report of the Surgeon General. [Atlanta, Ga.]: Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; Washington, DC: For sale by the Supt. of Docs., U.S. G.P.O.; 2004.

6. Tobacco Use and Dependence Guideline Panel. Treating tobacco use and dependence: 2008 update. Clinical practice guideline. US Department of Health and Human Services, Public Health Service, 2008. http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf.

7. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat

tobacco addiction: Cochrane update of 2012 reviews. *Addiction.* 2013;108:1711-1721.

8. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev.* 2013;5:CD009329.

9. Dacosta A, Guy JM, Tardy B, Gonthier R, Denis L, Lamaud M. Myocardial infarction and nicotine patch: a contributing or causative factor? *Eur Heart J.* 1993;14:1709-1711.

10. Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, Sherman SE, Cleveland M, Antonuccio DO, Hartman N, McGovern PG. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med.* 1996;335:1792-1798.

11. Haustein KO, Krause J, Haustein H, Rasmussen T, Cort N. Comparison of the effects of combined nicotine replacement therapy vs. cigarette smoking in males. *Nicotine Tob Res.* 2003;5:195-203.

12. Zevin S, Jacob P, 3rd, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. *Clin Pharmacol Ther.* 1998;64:87-95.

13. Rigotti NA, Thorndike AN, Regan S, McKool K, Pasternak RC, Chang Y, Swartz S, Torres-Finnerty N, Emmons KM, Singer DE. Bupropion for smokers hospitalized with acute cardiovascular disease. *Am J Med.* 2006;119:1080-1087.

14. Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, Silagy C, van Spiegel PI, Astbury C, Hider A, Sweet R. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. *Eur Heart J.* 2003;24:946-955.

15. Eisenberg MJ, Grandi SM, Gervais A, O'Loughlin J, Paradis G, Rinfret S, Sarrafzadegan N, Sharma S, Lauzon C, Yadav R, Pilote L. Bupropion for smoking cessation in patients hospitalized with acute myocardial infarction: a randomized, placebo-controlled trial. *J Am Coll Cardiol.* 2013;61:524-532.

16. 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;183:1359-1366.

17. 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.

18. FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of cardiovascular adverse events http://www.fda.gov/Drugs/DrugSafety/ucm330367.htm. *Dec 12, 2012.*

19. Toh S, Baker MA, Brown JS, Kornegay C, Platt R. Rapid assessment of cardiovascular risk among users of smoking cessation drugs within the US Food and Drug Administration's Mini-

Sentinel program. *JAMA Intern Med.* 2013;173:817-819.

20. Svanstrom H, Pasternak B, Hviid A. Use of varenicline for smoking cessation and risk of serious cardiovascular events: nationwide cohort study. *Bmj.* 2012;345:e7176.

21. Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO. Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tob Induc Dis.* 2010;8:8.

22. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation.* 2010;121:221-229.

23. Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *Jama.* 2012;308:1246-1253.

24. Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. *Ann Med.* 2012;44:588-597.

25. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343:d5928.

26. Meade MO, Cook RJ, Guyatt GH, Groll R, Kachura JR, Bedard M, Cook DJ, Slutsky AS, Stewart TE. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2000;161:85-90.

27. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177-188.

28. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med.* 2004;23:3105-3124.

29. Thorlund K, Thabane L, Mills EJ. Modelling Heterogeneity Variances in Multiple Treatment Comparison Meta-Analysis -- Are Informative Priors the Better Solution? *BMC Med Res Meth.* 2013;13.

30. Tonnesen P, Lauri H, Perfekt R, Mann K, Batra A. Efficacy of a nicotine mouth spray in smoking cessation: A randomised, double-blind trial. *Eur Resp J.* 2012;40:548-554.

31. Thomsen T, Tonnesen H, Okholm M, Kroman N, Maibom A, Sauerberg ML, Moller AM. Brief smoking cessation intervention in relation to breast cancer surgery: a randomized controlled trial. *Nicotine Tob Res.* 2010;12:1118-1124.

32. Shiffman S, Ferguson SG, Strahs KR. Quitting by gradual smoking reduction using nicotine

gum: a randomized controlled trial. *Am J Prev Med.* 2009;36:96-104 e101.

33. Oncken C, Cooney J, Feinn R, Lando H, Kranzler HR. Transdermal nicotine for smoking cessation in postmenopausal women. *Addict Behav.* 2007;32:296-309.

34. Wennike P, Danielsson T, Landfeldt B, Westin A, Tonnesen P. Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction.* 2003;98:1395-1402.

35. Etter JF, Laszlo E, Zellweger JP, Perrot C, Perneger TV. Nicotine replacement to reduce cigarette consumption in smokers who are unwilling to quit: a randomized trial. *J Clin Psychopharmacol.* 2002;22:487-495.

36. Glover ED, Glover PN, Franzon M, Sullivan CR, Cerullo CC, Howell RM, Keyes GG, Nilsson F, Hobbs GR. A comparison of a nicotine sublingual tablet and placebo for smoking cessation. *Nicotine Tob Res.* 2002;4:441-450.

37. Wallstrom M, Nilsson F, Hirsch JM. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. *Addiction.* 2000;95:1161-1171.

38. Hays JT, Croghan IT, Schroeder DR, Offord KP, Hurt RD, Wolter TD, Nides MA, Davidson M. Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled, and open label trials. *Am J Public Health.* 1999;89:1701-1707.

39. Tonnesen P, Paoletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, Rijcken B, Sawe U. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. *Eur Respir J.* 1999;13:238-246.

40. Blondal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *Eur Respir J.* 1997;10:1585-1590.

41. Sonderskov J, Olsen J, Sabroe S, Meillier L, Overvad K. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. *Am J Epidemiol.* 1997;145:309-318.

42. Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *Bmj.* 1995;311:363-366.

43. Schneider NG, Olmstead R, Mody FV, Doan K, Franzon M, Jarvik ME, Steinberg C. Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. *Addiction.* 1995;90:1671-1682.

44. Hjalmarson A, Franzon M, Westin A, Wiklund O. Effect of nicotine nasal spray on smoking cessation. A randomized, placebo-controlled, double-blind study. *Arch Intern Med.* 1994;154:2567-2572.

45. Sutherland G, Stapleton JA, Russell MA, Jarvis MJ, Hajek P, Belcher M, Feyerabend C. Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet.* 1992;340:324-329.

46. Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnersen AB, Forchammer H, Stockner M. Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. *N Engl J Med.* 1988;318:15-18.

47. Planer D, Lev I, Elitzur Y, Sharon N, Ouzan E, Pugatsch T, Chasid M, Rom M, Lotan C. Bupropion for smoking cessation in patients with acute coronary syndrome. *Arch Intern Med.* 2011;171:1055-1060.

48. McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Fiore MC, Baker TB. A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. *Nicotine Tob Res.* 2008;10:717-729.

49. Covey LS, Glassman AH, Jiang H, Fried J, Masmela J, LoDuca C, Petkova E, Rodriguez K. A randomized trial of bupropion and/or nicotine gum as maintenance treatment for preventing smoking relapse. *Addiction.* 2007;102:1292-1302.

50. Evins AE, Cather C, Culhane MA, Birnbaum A, Horowitz J, Hsieh E, Freudenreich O, Henderson DC, Schoenfeld DA, Rigotti NA, Goff DC. 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. *J Clin Psychopharmacol.* 2007;27:380-386.

51. Fossati R, Apolone G, Negri E, Compagnoni A, La Vecchia C, Mangano S, Clivio L, Garattini S. A double-blind, placebo-controlled, randomized trial of bupropion for smoking cessation in primary care. *Arch Intern Med.* 2007;167:1791-1797.

52. 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. *Arch Pediatr Adolesc Med.* 2007;161:1068-1074.

53. Uyar M, Filiz A, Bayram N, Elbek O, Herken H, Topcu A, Dikensoy O, Ekinci E. A randomized trial of smoking cessation. Medication versus motivation. *Saudi Med J.* 2007;28:922-926.

54. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *Jama.* 2006;296:47-55.

55. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *Jama.* 2006;296:56-63.

56. Puska PM, Barrueco M, Roussos C, Hider A, Hogue S. The participation of health professionals in a smoking-cessation programme positively influences the smoking cessation advice given to patients. *Int J Clin Pract.* 2005;59:447-452.

57. Zellweger JP, Boelcskei PL, Carrozzi L, Sepper R, Sweet R, Hider AZ. Bupropion SR vs placebo for smoking cessation in health care professionals. *Am J Health Behav.* 2005;29:240-249.

58. Dalsgareth OJ, Hansen NC, Soes-Petersen U, Evald T, Hoegholm A, Barber J, Vestbo J. A multicenter, randomized, double-blind, placebo-controlled, 6-month trial of bupropion hydrochloride sustained-release tablets as an aid to smoking cessation in hospital employees. *Nicotine Tob Res.* 2004;6:55-61.

59. ZYB400030:A Multi-centre, Randomised, Double-Blind, Placebo controlled study to evaluate the efficacy and tolerability of bupropion hydrochloride (SR) sustained release versus placebo as an aid to smoking cessation in a population of smokers with Chronic Obstructive Pulmonary Disease. http://search.gskclinicalstudyregister.com/search?q=ZYB40030&entqr=0&output=xml_no_dtd&sort=date%3AD%3AL%3Ad1&ud=1&client=default_frontend&oe=UTF-8&ie=UTF-8&proxystylesheet=default_frontend&site=gsktrials&btnG.x=40&btnG.y=8; 2003. http://search.gskclinicalstudyregister.com/search?q=ZYB40030&entqr=0&output=xml_no_dtd&sort=date%3AD%3AL%3Ad1&ud=1&client=default_frontend&oe=UTF-8&ie=UTF-8&proxystylesheet=default_frontend&site=gsktrials&btnG.x=40&btnG.y=8.

60. George TP, Vessicchio JC, Termine A, Bregartner TA, Feingold A, Rounsaville BJ, Kosten TR. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry*. 2002;52:53-61.

61. ZYB 30011:A multicentre, randomised, double- blind, placebo controlled study to evaluate the efficacy and tolerability of bupropion hydrochloride (SR) sustained release (2 x 150mg per day) versus placebo as an aid to smoking cessation in smokers with at least one cardiovascular (CV) risk factor. http://www.gskclinicalstudyregister.com/result_detail.jsp?protocolId=ZYB+30011&studyId=8B8951A0-176B-455E-93DB-24C4C2A3130F&compound=bupropion; 2002. http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=ZYB+30011&studyId=8B8951A0-176B-455E-93DB-24C4C2A3130F&compound=bupropion.

62. Gonzales DH, Nides MA, Ferry LH, Kustra RP, Jamerson BD, Segall N, Herrero LA, Krishen A, Sweeney A, Buaron K, Metz A. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther.* 2001;69:438-444.

63. Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, Sachs DP, Wolter TD, Buist AS, Johnston JA, White JD. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. *Ann Internal Med.* 2001;135:423-433.

64. Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, Gonzales D, Dozier G, Patel MK, Jamerson B. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet.* 2001;357:1571-1575.

65. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, Farrerons J, Karasik A, Mellstrom D, Ng KW, Stepan JJ, Powles TJ, Morrow M, Costa A, Silfen SL, Walls EL, Schmitt H, Muchmore DB, Jordan VC, Ste-Marie LG. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat.* 2001;65:125-134.

66. ZYB40005:The effect of sustained-release bupropion HCl vs. placebo as an aid to smoking reduction leading to cessation among smokers unwilling and unable to quit smoking. http://www.gskclinicalstudyregister.com/result_detail.jsp?protocolId=ZYB40005&studyId=1F130EA2-084E-485B-BC49-9878EE56D89D&compound=bupropion; 2001. http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=ZYB40005&studyId=1F130EA2-084E-485B-BC49-9878EE56D89D&compound=bupropion.

67. SMK20001:A Multi-Center, Double-Blind, Double-Dummy, Placebo-Controlled, Randomized, Parallel Group, Dose Response Evaluation of a New Chemical Entity (NCE) and ZYBAN (bupropion hydrochloride) Sustained Release (300mg/day) versus Placebo As Aids to Smoking Cessation. http://www.gskclinicalstudyregister.com/result_detail.jsp?protocolId=SMK20001&studyId=26B17828-34B1-4C9B-B480-442C066D2118&compound=bupropion; 2000. http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=SMK20001&studyId=26B17828-34B1-4C9B-B480-442C066D2118&compound=bupropion. Accessed http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=SMK20001&studyId=26B17828-34B1-4C9B-B480-442C066D2118&compound=bupropion.

68. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med.* 1999;340:685-691.

69. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, Croghan IT, Sullivan PM. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med.* 1997;337:1195-1202.

70. ZYBAKIA402:A single center evaluation of Wellbutrin (bupropion hydrochloride) versus placebo as an aid to smoking cessation (study 402). http://www.gskclinicalstudyregister.com/result_detail.jsp?protocolId=ZYBAKIA402&studyId=6D3EA840-19AC-4D0B-BFD5-8F8E8E314634&compound=bupropion; 1994. http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=ZYBAKIA402&studyId=6D3EA840-19AC-4D0B-BFD5-8F8E8E314634&compound=bupropion. Accessed http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=ZYBAKIA402&studyId=6D3EA840-19AC-4D0B-BFD5-8F8E8E314634&compound=bupropion.

71. AKIA401:A single-center evaluation of Wellbutrin (bupropion hydrochloride) versus placebo as an aid to smoking cessation in heavy smokers (study 401). http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=AKIA401&studyId=368102E5-41ED-45C6-A7C0-CAD17CBCF764&compound=bupropion; 1992. http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=AKIA401&studyId=368102E5-41ED-45C6-A7C0-CAD17CBCF764&compound=bupropion. Accessed http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=AKIA401&studyId=368102E5-41ED-45C6-A7C0-CAD17CBCF764&compound=bupropion.

72. Tonnesen P, Mikkelsen K. Varenicline to stop long-term nicotine replacement use: a double-blind, randomized, placebo-controlled trial. *Nicotine Tob Res.* 2013;15:419-427.

73. Rennard S, Hughes J, Cinciripini PM, Kralikova E, Raupach T, Arteaga C, St Aubin LB, Russ C, Flexible Quit Date Study G. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. *Nicotine Tob Res.* 2012;14:343-350.

74. Wong J, Abrishami A, Yang Y, Zaki A, Friedman Z, Selby P, Chapman KR, Chung F. A perioperative smoking cessation intervention with varenicline: A double-blind, randomized, placebo-controlled trial. *Anesthesiology.* 2012;117:755-764.

75. Garza D, Murphy M, Tseng LJ, Riordan HJ, Chatterjee A. A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo. *Biol Psychiatry.* 2011;69:1075-1082.

76. Steinberg MB, Randall J, Greenhaus S, Schmelzer AC, Richardson DL, Carson JL. Tobacco dependence treatment for hospitalized smokers: a randomized, controlled, pilot trial using varenicline. *Addict Behav.* 2011;36:1127-1132.

77. Tashkin DP, Rennard S, Hays JT, Ma W, Lawrence D, Lee TC. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. *Chest.* 2011;139:591-599.

78. Bolliger CT, Issa JS, Posadas-Valay R, Safwat T, Abreu P, Correia EA, Park PW, Chopra P. Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2011;33:465-477.

79. Fagerstrom K, Gilljam H, Metcalfe M, Tonstad S, Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *Bmj.* 2010;341:c6549.

80. Aubin HJ, Bobak A, Britton JR, Oncken C, Billing CB, Jr., Gong J, Williams KE, Reeves KR. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax.* 2008;63:717-724.

81. Niaura R, Hays JT, Jorenby DE, Leone FT, Pappas JE, Reeves KR, Williams KE, Billing CB, Jr. The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial. *Curr Med Res Opin.* 2008;24:1931-

1941.

82. Nakamura M, Oshima A, Fujimoto Y, Maruyama N, Ishibashi T, Reeves KR. Efficacy and tolerability of varenicline, an alpha4beta2 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. *Clin Ther.* 2007;29:1040-1056.

83. Tsai ST, Cho HJ, Cheng HS, Kim CH, Hsueh KC, Billing CB, Jr., Williams KE. A randomized, placebo-controlled trial of varenicline, a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. *Clin Ther.* 2007;29:1027-1039.

84. Williams KE, Reeves KR, Billing CB, Jr., Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. *Curr Med Res Opin.* 2007;23:793-801.

85. Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, Reeves KR. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med.* 2006;166:1561-1568.

86. Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, Anziano R, Reeves K. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med.* 2006;166:1571-1577.

87. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *Jama.* 2006;296:64-71.

88. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *Bmj.* 2013;346:f2914.

89. Matthew TP, Herity NA. Acute myocardial infarction soon after nicotine replacement therapy. *QJM.* 2001;93:503-504.

90. Ottervanger JP, Festen JM, de Vries AG, Stricker BH. Acute myocardial infarction while using the nicotine patch. *Chest.* 1995;107:1765-1766.

91. Gourlay SG, Forbes A, Marriner T, McNeil JJ. Predictors and timing of adverse experiences during trandsdermal nicotine therapy. *Drug Saf.* 1999;20:545-555.

92. Benowitz NL, Goniewicz ML. The Regulatory Challenge of Electronic Cigarettes. *Jama.* 2013;310:685-686.

93. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, Jacob P, 3rd, Benowitz N. Levels of selected

carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco control.* 2013. [Epub ahead of print]

94. Ottawa Model for Smoking Cessation. http://www.ottawamodel.ca.

95. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease : a report of the Surgeon General. – Rockville, MD : Dept. of Health and Human Services, Public Health Service, Office of Surgeon General, 2010. 2010.

96. Bradburn MJ, Deeks JJ, Berlin JA. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med.* 2007;26:53-77.

97. Naylor C, Chen E, Strauss B. Measured Enthusiasm: Does the Method of Reporting Trial Results Alter Perceptions of Therapeutic Effectiveness? *Ann Intern Med.* 1992;117:916-921.

98. Prochaska JJ, Hilton JF. Choice of summary statistics: relative and absolute measures. *Bmj.* 2013;346:f1092.

99. Roose SP. Considerations for the use of antidepressants in patients with cardiovascular disease. *Am Heart J.* 2000;140:84-88.

100. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG. Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry.* 1991;148:512-516.

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Table 1. Characteristics of included trials of nicotine replacement therapy, bupropion, and varenicline.

Trial	Participant characteristics	Cigarettes per day mean (SD or range); median*	Years Smoking mean (SD or range); median*	Duration of the treatment (wks)	Whole Study Duration (mth)	Arm	Co-Treatment	Age mean (SD or range); median*	Male (%)	n	Reported CV Outcomes
					Nicotine Replacement Therapy						
Tonnesen et al 2012[30]	Healthy	22.7(8.8)	NR	52	NR	Placebo	Counseling	46.2(11.3)	54.7	161	Myocardial Infarction
						Spray 1 mg	Counseling	47.0(10.9)	56.9	318	
Thomsen et al 2010[31]	Breast Cancer Surgery	NR	NR	2	12	Placebo	Counseling	56.5(36-82)	0.0	62	CVD event
						NRT	Counseling	57.5(35-79)	0.0	58	
Shiffman et al 2009[32]	Healthy	25(8)	26(12)	12	6	Placebo 2mg	Counseling	42.2(13.3)	34.5	817	Heart Rate
						Gum 2 mg	Counseling	42.1(13.0)	37.2	819	
						Placebo 4mg	Counseling	46.3(11.4)	47.8	830	
						Gum 4 mg	Counseling	46.1(11.3)	52.4	830	
Oncken et al 2007[33]	Post Menopausal Women	21(8)	33(10)	12	12	Placebo	Group Counseling	56.6(6.9)	0.0	95	Hospitalized Chest Pain
						Patch 21 mg	Group Counseling	54.0(6.9)	0.0	57	
Wennike et al 2003[34]	Healthy	24(7)	29(9)	52	24	Placebo 2 mg		44.0(10.0)	41	68	Heart Palpitations
						Gum 2 mg		45.0(10.0)	35	65	
						Placebo 4 mg		44.0(10.0)	41	138	
						Gum 4 mg		45.0(10.0)	35	140	
Etter et al 2002[35]	Healthy	30(10)	≥3	24	6	Placebo		41.7	49	269	Stroke
						No Treatment		42.9	44	389	
						NRT 2,15,0.5 mg		43.2	54	265	
Glover et al 2002[36]	Healthy	29(16)	25(11)	12-24	12	Placebo		41.8(11.6)	44.6	121	Atherosclerotic CVD
						Tablet 2 mg		43.9(10.0)	47.5	120	
Wallstrom et al 2000[37]	Healthy	19(6)	26(10)	12-24	12	Placebo		44.7(11.4)	45.2	124	Atrial Fibrillation
						Tablet 2 mg		44.5(11.6)	36.6	123	
						Gum 4 mg		41.4(11.7)	51.7	203	
Hays et al 1999[38]	Healthy	≥15	26(12)	6	6	Placebo		44.1(11.6)	52.5	322	Acute Myocardial Infarction
						Patch 22 mg		43.5(11.2)	48.6	321	
						Patch 10-15 mg		28.2(4.9)	0.0	124	
Tonnesen et al 1999[39]	Healthy	27(10)	23(10)	8	12	Placebo	Advice Brochure	41.0(10.0)	52.0	714	Heart Palpitations, Tachycardia, Acute Myocardial Infarction
						Patch 15 mg	Advice Brochure	41.0(10.0)	51.0	716	

						Patch 25 mg	Advice Brochure	41.0(10.0)	53.0	715	
Blondal et al 1997[40]	Healthy	25(4-50)	2.7(1-5)	12	24	Placebo		42(21-67)	38.5	78	Heart Palpitations
						Spray 1 mg		42.0(22-67)	50.6	79	
Sonderskov et al 1997[41]	Healthy	≥20	21(11)	12	6	Placebo 14mg		38.9(13.7)	58.3	125	Heart Palpitations, Chest Pain
						Patch 14mg		38.2(12.9)	41.7	119	
						Placebo 21mg		39.9(10.9)	49.2	142	
						Patch 21mg		39.1(10.8)	50.8	132	
Joseph et al 1996[10]	Cardiac Disease	28	44	10	6	Placebo	Behaviour Counseling	60.0	98.6	290	Stroke, Acute Myocardial Infarction, Atrial Fibrillation, Heart Failure, CVD
						Patch 7,14,21 mg	Behaviour Counseling	61.0	98.6	294	
Gourlay et al 1995[42]	Healthy	27(10)	23(10)	12	6	Placebo	Behavioral Counseling	41.0(10.4)	42.4	314	Heart Palpitations, Cardiac Arrhythmia
						Patch 7-21 mg	Behavioral Counseling	41.0(10.4)	42.4	315	
Schneider et al 1995[43]	Healthy	29(10)	22(10)	24	12	Placebo		39.7(7.2)	58.0	127	Heart Palpitations
						Spray 1 mg		39.9(7.7)	52.0	128	
Hjalmarson et al 1994[44]	Healthy	21(10-70)	26(10)	12	12	Placebo	Group Counseling	44.9(11.1)	43.1	123	Pounding Heart
						Spray 1 mg	Group Counseling	44.9(11.5)	42.4	125	
						Gum 2 mg	Behavior Modification Program	38.1(8.8)	76.0	76	
Sutherland et al 1992[45]	Healthy	26(10)	22(10)	4	12	Placebo		40.4(9.4)	34.2	111	Pounding Heart
						Spray 1 mg		38.9(9.4)	37.1	116	
Tonnesen et al 1988[46]	Healthy + Chronic Dis.	≥10	NR	6	24	Placebo	Counseling	45.5(11.7)	42.0	53	Heart Palpitations
						Gum 2 mg	Counseling	44.9(10.4)	47.0	60	
Bupropion											
Eisenberg et al 2013[15]	Acute Myocardial Infarction	23(11)	33(12)	9	12	Placebo	Counseling	53.4(10.3)	83.2	200	Acute Myocardial Infarction, Unstable Angina, Atrial fibrillation, Cardiac Arrest, Tachycardia, Cardiogenic Shock, Congestive Heart Failure, Thromboendarterectomy
						Bupropion 300 mg	Counseling	54.5(10.4)	83.8	192	
Planer et al 2011[47]	Acute Coronary Syndrome	31(16)	NR	8	12	Placebo	Counseling	51.5(9)	82.7	75	Acute Myocardial Infarction, Atrial Fibrillation
						Bupropion 300 mg	Counseling	52.4(11)	77	74	

McCarthy et al 2008[48]	Healthy	22(10)	25(12)	8	12	Placebo	No Counseling	39.4(11.3)	46	116	Stroke, Aneurysm
						Placebo	Counseling	37.8(12.8)	47.9	121	
						Bupropion 300 mg	No Counseling	41.0(12.6)	50.9	116	
						Bupropion 300 mg	Counseling	36.8(11.4)	54	113	
Covey et al 2007[49]	Healthy	21(9)	NR	20	12	Placebo	Placebo gum	42.5(10.6)	53.5	71	Acute Myocardial Infarction
						Placebo	Nicotine gum	43.5(10.8)	54.2	72	
						Bupropion 300 mg	Placebo gum	43.7(10.8)	53.4	73	
						Bupropion 300 mg	Nicotine gum	40.3(9.9)	57.5	73	
Evins et al 2007[50]	Schizophrenia	26(12)	26(11)	12	6	Placebo	Nicotine Patch and Gum	43.6(10.9)	NR	26	Heart Palpitations
						Bupropion 300 mg	Nicotine Patch and Gum	44.8(9.2)	NR	25	
Fossati et al 2007[51]	Healthy	23(9)	≥1	7	12	Placebo		48.5 (42-56) [IQR]*	55.4	193	Acute Myocardial Infarction
						Bupropion 300 mg		49.4(40-57) [IQR]*	62	400	
Muramoto et al 2007[52]	Adolescent	11(9) [IQR]*	4*	6	6	Placebo	Counseling	16*	58.3	103	Tachycardia
						Bupropion 150 mg	Counseling	16*	46.7	105	
						Bupropion 300 mg	Counseling	16*	57.7	104	
Uyar et al 2007[53]	Pulmonary Disease	≥10	≥1	6	6	Advice		36.0(10.6)	70	31	Tachycardia
						Bupropion 300 mg		36.0(10.5)	88	50	
						Patch 7-21 mg		36.3(12.7)	80.0	50	
Gonzales et al 2006[54]	Healthy	21(9)	24(12)	12	12	Placebo	Counseling	42.6(11.8)	54.1	344	Acute Myocardial Infarction, Atrial Fibrillation
						Bupropion 300 mg	Counseling	42.0(11.7)	58.4	329	
						Varenicline 2 mg/d	Counseling	42.5(11.1)	50	352	
Jorenby et al 2006[55]	Healthy	22(12)	25(12)	12	12	Placebo	Counseling	42.3(11.6)	58.1	341	Acute Myocardial Infarction, Coronary Artery Occlusion
						Bupropion 300 mg	Counseling	42.9(11.9)	60.2	342	
						Varenicline 2 mg/d	Counseling	44.6(11.4)	55.2	344	
Rigotti et al 2006[13]	CVD	22(12)	38(11)	12	12	Placebo	Counseling	54.9(9.7)	69	124	Death in CVD
						Bupropion 300 mg	Counseling	56.7(9.7)	69	124	
Puska et al 2005[56]	Healthy	23(8)	≥1	7	12	Placebo	Motivational Support	40.3(9.1)	36	170	Stroke
						Bupropion 300 mg	Motivational Support	40.3(8.9)	36	517	
Zellweger et al 2005[57]	Healthy	23(8)	26(16)	7	12	Placebo		40.3(9.1)	36	170	Stroke
						Bupropion 300 mg		40.3(8.9)	36	517	

Dalsgareth et al 2004[58]	Healthy	19(6)	27(13)	7	6	Placebo		44.3(9.4)	25.4	114	Tachycardia, Acute Myocardial Infarction (death)
						Bupropion 300 mg		42.5(9.9)	25.3	221	
Tonstad et al 2003[14]	CVD	25(12)	50(25)	7	12	Placebo		55.1(9.0)	79	313	Angina Pectoris, Heart Palpitations
						Bupropion 300 mg		55.6(9.2)	74	313	
ZYB40030 2003[59]	COPD	NR	NR	9	9wks	Placebo		55(9.5)	63.4	159	Acute Myocardial Infarction, Angina
						Bupropion 300 mg		55(9.5)	63.4	155	
George et al 2002[60]	Schizophrenia	24(11)	NR	10	6	Placebo		40.9(9.4)	50	16	Irregular Heartbeat
						Bupropion 300 mg		45.4(11.9)	62.5	16	
ZYB30011 2002[61]	>1 CVD risk factor	≥10	≥1	7	6	Placebo		49.2(9.9)	62.2	127	Heart Palpitations
						Bupropion 300 mg		47.9(9.7)	69.3	127	
Gonzales et al 2001[62]	Healthy	≥15	NR	12	6	Placebo		45.5(11.2)	45	224	Stroke, Acute Myocardial Infarction, Atrial Fibrillation, Coronary Artery Disorder
						Bupropion 300 mg		44.5(11.8)	52	226	
Hays et al 2001[63]	Healthy	27(10)	≥1	45	24	Placebo		45.4(9.2)	52.1	215	Angina, Stroke, Acute Myocardial Infarction (death)
						Bupropion 300 mg		47.0(9.7)	45.3	214	
Tashkin et al 2001[64]	COPD	28(11)	51(24)	12	6	Placebo		54.5(9.5)	55.1	205	Stroke, Cardiac Arrest, Myocardial Infarction,
						Bupropion 300 mg		53.2(9.0)	54.9	206	
ZYB40001 2001[65]	Healthy	≥15	≥1 month	12	3	Placebo	Behavioural Support	43.8(22-68)	50.3	143	Stroke
						Bupropion 300 mg	Behavioural Support	43.7(19-67)	46.8	141	
ZYB40005 2001[66]	NR	NR	NR	24	12	Placebo		41.8(18-71)	53	304	Acute Myocardial Infarction, Congestive Heart Failure
						Bupropion 300 mg		42.4(19-69)	57.4	305	
SMK20001 2000[67]	Healthy	≥15	≥1	7	12	Placebo		42.1(10.2)	51	143	Stroke, Acute Myocardial Infarction
						Bupropion 300 mg		42.9(10.2)	52.4	143	
Jorenby et al 1999[68]	Healthy	26(11)	26(11)	9	12	Placebo	None	42.7(10.2)	41.2	160	Acute Myocardial Infarction (death)
						No Treatment	Patch	44.0(10.9)	48.4	244	
						Bupropion 300 mg	None	42.3(10.2)	48.4	244	
						Bupropion 300 mg	Patch	43.9(11.6)	50.6	245	
Hurt et al 1997[69]	Healthy	27(10)	≥1	7	12	Placebo		43.0(10.7)	40.5	153	Cardiac Arrest (Death)
						Bupropion 100 mg		44.1(10.5)	41.8	153	
						Bupropion 150 mg		42.3(11.3)	49.7	153	
						Bupropion 300 mg		45.0(11.8)	49.4	156	
ZYBAK1A402 1994[70]	Healthy	≥20	NR	12	12	Placebo	Counseling	54(11.3)	86.3	95	Tachycardia
						Bupropion 300 mg	Counseling	51(11.8)	82.1	95	
AKIA401 1992[71]	Healthy	≥20	NR	12	12	Placebo	Counseling	58.0(8.0)	100	25	Fatal Hypotension (death)
						Bupropion 300 mg	Counseling	55(9.3)	100	23	

Varenicline											
Tonnesen et al 2013[72]	Healthy	23(9)	NR	12	52	Placebo	Counseling	55.6(9.1)	49.3	69	Stroke, Myocardial Infarction
						Varenicline 2 mg/d	Counseling	53.6(8.2)	42.9	70	
Rennard et al 2012[73]	Healthy	21(10-70)	25(2-57)	12	6	Placebo	Counseling	43.2(12.2)	59.6	166	Carotid Artery Stenosis
						Varenicline 2 mg/d	Counseling	43.9(12.5)	60	493	
Wong et al 2012[74]	Perioperative	17(8)	≥1	12	12	Placebo	Counseling	53.3(11.4)	50.4	135	Myocardial Infarction, Ischemia, Stroke, Deep Vein Thrombosis, Bradycardia
						Varenicline 0.5-2 mg/d	Counseling	51.9(11.8)	55.0	151	
Garza et al 2011[75]	Healthy	22(10-50)	17(3-49)	12	3	Placebo	Counseling	33.8(8.8)	72.7	55	Heart Palpitations
						Varenicline 2 mg/d	Counseling	33.4(11.8)	60	55	
Steinberg et al 2011[76]	Hospitalized Patients	≥10	NR	12	6	Placebo	Counseling	51(22-78)	60	40	Heart Palpitation, Tachycardia, Stroke, Acute Myocardial Infarction
						Varenicline 2 mg/d	Counseling	51(22-78)	59	39	
Tashkin et al 2011[77]	Mild to moderate COPD	24(10-99)	40(11-67)	12	12	Placebo	Counseling	57.1(9.0)	62.2	251	Angina Pectoris, Stroke, Acute Myocardial Infarction
						Varenicline 2 mg/d	Counseling	57.2(9.1)	62.5	248	
Bolliger et al 2010[78]	Healthy	24(10-90)	26(1-58)	12	6	Placebo	Counseling	43.9(10.8)	65.7	198	Tachycardia, Atrial Fibrillation
						Varenicline 2 mg/d	Counseling	43.1(10.8)	57.7	390	
Fagerstrom et al 2010[79]	Healthy	NR	22(11)	12	6	Placebo	Counseling	43.9(12.0)	89.9	218	Acute Myocardial Infarction
						Varenicline 2 mg/d	Counseling	43.9(12.0)	88.7	214	
Rigotti et al 2010[22]	Cardiovascular Disease	23(10-60)	40(5-63)	12	12	Placebo	Counseling	55.9(8.3)	82.2	359	Hospitalized Angina Rectoris, Coronary Revascularization, Acute Myocardial Infarction, Stroke
						Varenicline 2 mg/d	Counseling	57.0(8.6)	75.2	355	
Aubin et al 2008[80]	Healthy	23(11-80)	25(1-62)	12	9	Varenicline 2 mg/d	Counseling	42.9(10.5)	48.4	376	Myocardial Infarction
						Patch 7-21 mg	Counseling	42.9(12.0)	50	370	
Niaura et al 2008[81]	Healthy	22(6-60)	25(2-50)	12	12	Placebo	Education Booklet	42.1(11.7)	53.5	160	Acute Myocardial Infarction, Atrial Fibrillation,
						Varenicline 0.5-2 mg/d	Education Booklet	41.5(11.3)	50.3	160	
Nakamura et al 2007[82]	Healthy	24(10)	20(11)	12	12	Placebo	Counseling	39.9(12.3)	76	154	Angina Rectoris
						Varenicline 0.5mg/d	Counseling	40.2(12.3)	72.7	153	
						Varenicline 1mg/d	Counseling	39.0(12.0)	71.1	156	
						Varenicline 2 mg/d	Counseling	40.1(11.6)	79.2	156	
Tsai et al 2007[83]	Healthy	23(10-60)	21(3-52)	12	6	Placebo	Counseling	40.9(11.1)	92.7	124	Unstable Angina
						Varenicline 2 mg/d	Counseling	39.7(9.3)	84.9	126	

Williams et al 2007[84]	Healthy	23(10-90)	30(4-57)	52	12	Placebo	Counseling	46.6(12.1)	48.4	126	CVD, Acute Myocardial Infarction
						Varenicline 2 mg/d	Counseling	48.2(12.3)	50.6	251	
Nides et al 2006[85]	Healthy	20(8)	24(11)	7	12	Placebo	Counseling	41.6(10.4)	52	127	Stroke
						Varenicline 0.3 mg/d	Counseling	41.9(10.6)	50	128	
						Varenicline 1 mg/d	Counseling	42.9(10.5)	43.7	128	
						Varenicline 2 mg/d	Counseling	41.9(9.8)	50.4	127	
Oncken et al 2006[86]	Healthy	21(9)	25(10)	12	12	Placebo	Counseling	43.0(9.4)	51.9	129	Unstable Angina, Tachycardia
						Varenicline 1 mg/d	Counseling	43.2	49.1	259	
						Varenicline 2 mg/d	Counseling	43	48.6	259	
Tonstad et al 2006[87]	Healthy	21(7)	28(10)	12	12	Placebo		45.3(10.4)	48.3	607	
						Varenicline 2 mg/d		45.4(10.4)	50.2	603	

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Table 2. Estimated relative risk (RR) and 95% confidence intervals (CIs) produced by random effects pair-wise meta-analysis for cardiovascular events in smoking cessation RCTs.

Number of Studies	Comparison	All CV Events			MACE Events		
		Events	RR	I^2	Events	RR	I^2
All trials							
21 RCTs[10, 30-46, 49, 53, 68]	NRT vs placebo	202/6329 vs. 83/5318	1.81 (1.35-2.43)	0%	12/6329 vs. 7/5318	1.38 (0.58-3.26)	0%
27 RCTs[13-15, 47-49, 51-71]	Bupropion vs placebo	50/5947 vs. 42/4455	1.03 (0.71-1.50)	0%	15/5947 vs. 25/4455	0.57 (0.31-1.04)	0%
18 RCTs[22, 54, 55, 72-79, 81-87]	Varenicline vs placebo	63/5469 vs. 41/3603	1.24 (0.85-1.81)	0%	22/5469 vs. 13/3603	1.44 (0.73-2.83)	0%
2 RCTs[54, 55]	Bupropion vs varenicline	1/686 vs. 2/696	0.74 (0.05-10.5)		1/686 vs. 0/696	3.07 (0.12-75.09)	
3 RCTs[49, 53, 68]	Bupropion vs NRT	4/367 vs. 2/366	1.40 (0.25-7.82)	2%	0/367 vs. 1/366	0.34 (0.01-7.94)	
1 RCT[80]	Varenicline vs NRT	0/378 vs. 2/379	0.20 (0.01-4.16)		0/378 vs. 2/379	0.20 (0.01-4.16)	
High risk patients only		***k=13***			***k=9***		
3 RCTs[10, 46, 53]	NRT vs placebo	33/454 vs. 26/374	1.24 (0.77-2.02)		6/454 vs. 4/374	1.48 (0.42-5.19)	**NA**
8 RCTs[13-15, 47, 53, 59, 61, 64]	Bupropion vs placebo	27/1241 vs. 25/1234	1.04 (0.59-1.83)	0%	9/1241 vs. 15/1234	0.63 (0.28-1.41)	0%
3 RCTs[22, 74, 77]	Varenicline vs placebo	30/754 vs. 26/745	1.15 (0.69-1.92)		14/754 vs. 11/745	1.35 (0.61-3.01)	0%
	Bupropion vs varenicline		NA			NA	
1 RCT[53]	Bupropion vs NRT	3/50 vs. 0/50	7 (0.37-132.10)		0/50 vs. 0/50	NA	
	Varenicline vs NRT		NA			NA	

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Table 3. Estimated relative risk (RR) and 95% credibility intervals (CrI) from random effects network meta-analysis for cardiovascular events in smoking cessation RCTs.

Comparison	All-CVD events	MACE
NRT vs placebo	2.29 (1.39-3.82)	1.95 (0.92-4.30)
Bupropion vs placebo	0.98 (0.54-1.73)	0.45 (0.21-0.85)
Varenicline vs placebo	1.30 (0.79-2.23)	1.34 (0.66-2.66)
Bupropion vs varenicline	0.76 (0.33-1.73)	0.33 (0.16-0.87)
Bupropion vs NRT	0.43 (0.19-0.91)	0.23 (0.08-0.63)
Varenicline vs NRT	0.56 (0.25-1.27)	0.67 (0.26-1.90)
High risk populations (sensitivity analysis)		
NRT vs placebo	1.31 (0.58-3.32)	1.53 (0.38-6.24)
Bupropion vs placebo	1.06 (0.59-2.04)	0.48 (0.18-1.21)
Varenicline vs placebo	0.99 (0.45-1.88)	1.22 (0.44-2.90)
Bupropion vs varenicline	1.09 (0.46-2.92)	0.39 (0.11-1.49)
Bupropion vs NRT	0.81 (0.26-2.26)	0.31 (0.05-1.68)
Varenicline vs NRT	0.92 (0.34-2.19)	0.81 (0.13-4.20)

Figure Legends:

Figure 1. Flow diagram of randomized controlled trials selected for the meta-analysis of cardiovascular events associated with smoking cessation therapies.

Figure 2. Geometric distribution of the MTC analysis, including randomized trials of nicotine replacement therapy, bupropion, and varenicline. Nodes represent the study therapies. Links between the nodes represent direct comparisons from RCTs. The numbers beside the nodes represent the number of RCTs.

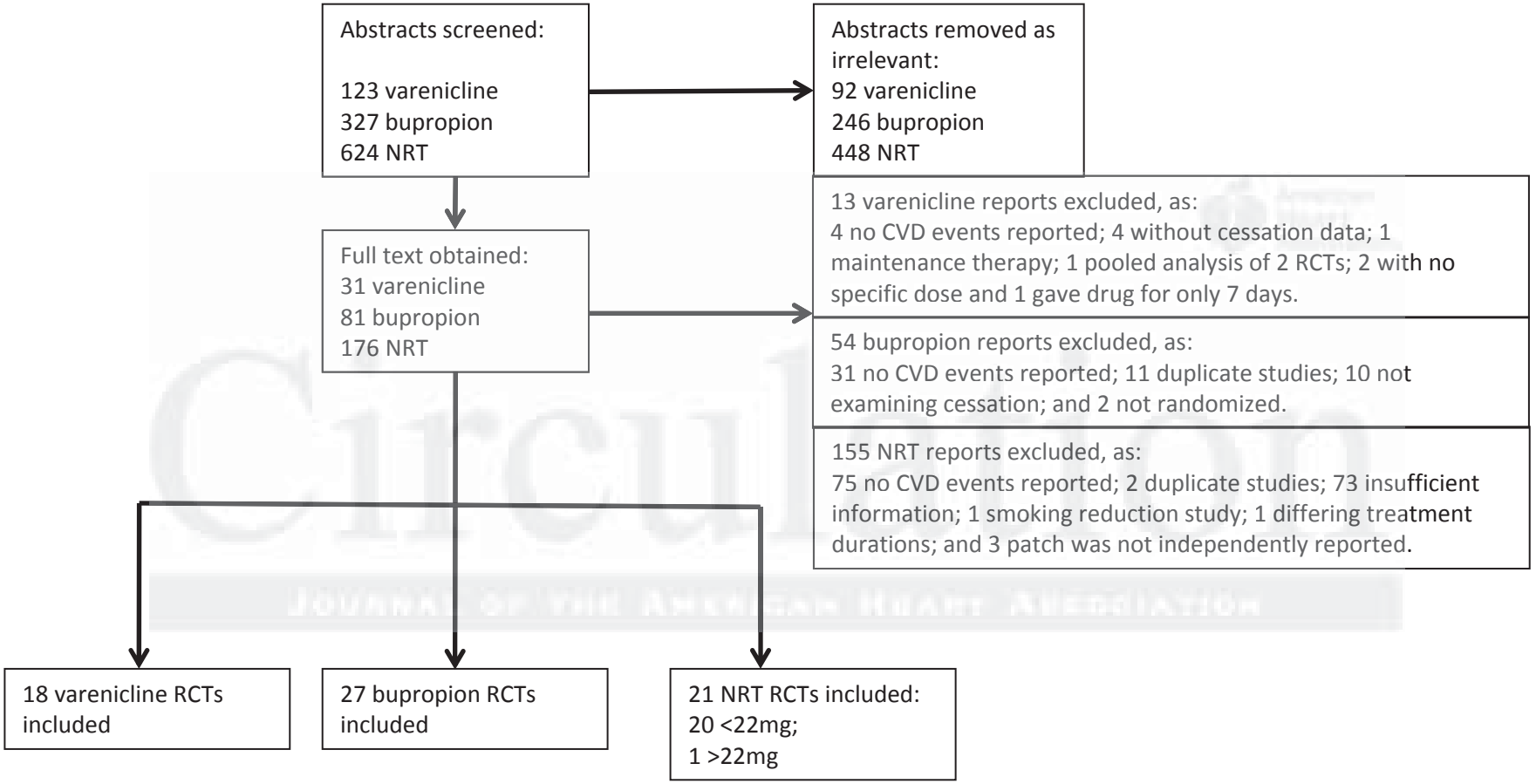

Figure 1

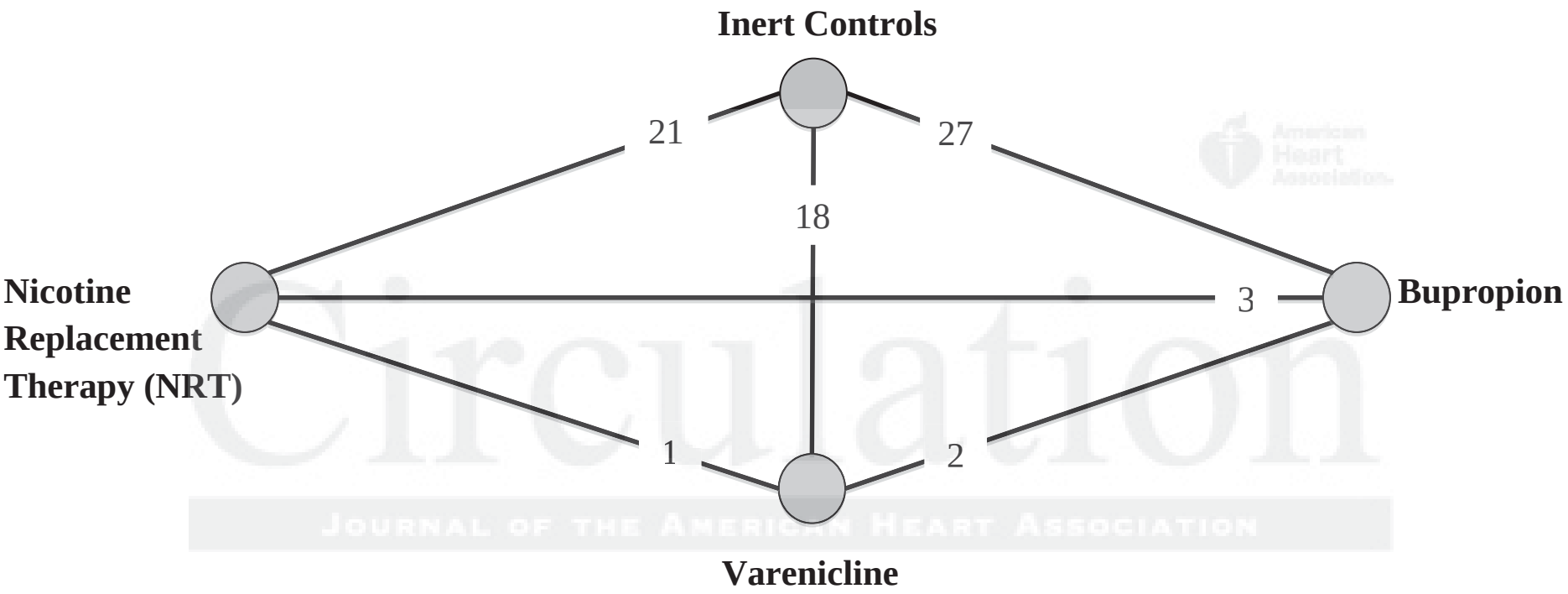

Figure 2

SUPPLEMENTAL MATERIAL

Appendix 1. Description of Bayesian Network meta-analysis.

We modeled log odds ratios using the conventional logistic regression network meta-analysis setup.[1] From this logistic regression model we produced relative risks for all comparisons, utilizing the pooled control group proportions (and pooled log odds). We accounted for unexplained variance by employing a random-effects approach. With rare event data, as was the case for the data, the between-study (heterogeneity) variance estimation can become upward biased in the Bayesian framework as the elicited prior variance distribution carries high probability mass for large values.[2] For this reason, we decided to use an empirically informed approach previously shown to be reliable.[2, 3] Sensitivity analyses examined what endpoints were driving the harmful events and whether the duration of the trials were associated with larger effect sizes. We estimated the posterior densities for all unknown parameters using Markov chain Monte Carlo methods for each model. We assessed convergence based on the Brooks-Gelman-Rubin criteria using three Markov chains and found that 20000 iterations were enough for reliable burn-in. All results for the network analysis are reported as posterior means with corresponding 95% credibility intervals (CrIs). Credibility intervals are the Bayesian equivalent of classical confidence intervals. We assessed the fit of our model using the Deviance Information Criterion (DIC), a measure of model fit that penalizes model complexity. The network results were assessed for consistency by comparing them with an adjusted indirect comparison[4] and with the pair-wise meta-analyses results. We evaluated incoherence between direct estimates and indirect estimates for statistical

differences. As ORs are statistically superior to RRs,[5] we conducted the network with OR as the effect size and converted the OR to RRs.

Analyses were conducted using Comprehensive Meta-analysis (version 2, http://www.meta-analysis.com) and WinBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge).

Appendix 2. Search strategy

(Ovid syntax)

1. random:.tw,sh,pt. OR placebo:.tw,sh.

2. (clinical trial OR controlled clinical trial).pt.

3. ((single or doubl: or tripl: or treb:) AND (blind:

or mask:)).tw,ab

4. OR/1 – 3

5. Tobacco Use Cessation Products [mesh]

6. nicotine OR NRT OR nicotine replacement

7. bupropion OR zyban

8. varenicline OR champix OR chantix

9. OR/5 – 8

10. smoking [mesh]

11. AND 9 AND 10

Supplemental Table 1. List of publications excluded due to non-reporting of CVD events.

Trial	Intervention
Ahluwalia et al 2002[6]	Bupropion
AK1A4010 2000[7]	Bupropion
Aubin et al 2004[8]	Bupropion
Brown et al 2007[9]	Bupropion
Cox et al 2012[10]	Bupropion
Evins et al 2001[11]	Bupropion
Evins et al 2005[12]	Bupropion
George et al 2008[13]	Bupropion
Grant et al 2007[14]	Bupropion
Haggstram et al 2006[15]	Bupropion
Hall et al 2002[16]	Bupropion
Hatsukami et al 2004[17]	Bupropion
Hertzberg et al 2001[18]	Bupropion
Holt et al 2005[19]	Bupropion
Hurt et al 2003[20]	Bupropion
Karam-Hage et al 2011[21]	Bupropion
Killen et al 2004[22]	Bupropion
Killen et al 2006[23]	Bupropion
Lerman et al 2002[24]	Bupropion
Myles et al 2004[25]	Bupropion
Piper et al 2007[26]	Bupropion
Piper et al 2009[27]	Bupropion

Schmitz et al 2007[28]	Bupropion
Schnoll et al 2010[29]	Bupropion
Sheng et al 2012[30]	Bupropion
Simon et al 2004[31]	Bupropion
Simon et al 2009[32]	Bupropion
Swanson et al 2003[33]	Bupropion
Tonnesen et al 2003[34]	Bupropion
Wagena et al 2005[35]	Bupropion
Weiner et al 2012[36]	Bupropion
Wittchen et al 2011[37]	Bupropion
Zernig et al 2008[38]	Bupropion
ZYBF4001 2002[39]	Bupropion
de Dios et al 2012[40]	Varenicline
Ebbert et al 2011[41]	Varenicline
Ferketich et al 2013[42]	Varenicline
Heydari et al 2012[43]	Varenicline
Hong et al 2011[44]	Varenicline
Hughes et al 2011[45]	Varenicline
Mitchell et al 2012[46]	Varenicline
Poling et al 2010[47]	Varenicline
Williams et al 2012 (NCT00644969)[48]	Varenicline
Tsukahara et al 2010[49]	Varenicline

Wang et al 2009[50]	Varenicline
Abelin et al 1989[51]	NRT
Areechon et al 1988[52]	NRT
Batra et al 2005[53]	NRT
Blondal et al 1989[54]	NRT
Blondal et al 1999[55]	NRT
Bohadana et al 2000[56]	NRT
Bolliger et al 2000[57]	NRT
British Thoracic Society et al 1983[58]	NRT
Buchkremer et al 1988[59]	NRT
Campbell et al 1991[60]	NRT
Campbell et al 1996[61]	NRT
Chou et al 2004[62]	NRT
Cinciripini et al 1996[63]	NRT
Coleman et al 2012[64]	NRT
Cooney et al 2009[65]	NRT
Croghan et al 2003[66]	NRT
Dale et al 1995[67]	NRT
Daughton et al 1991[68]	NRT
Daughton et al 1998[69]	NRT
Daughton et al 1999[70]	NRT
Davidson et al 1998[71]	NRT
Fagerstrom et al 1982[72]	NRT

Fiore et al 1994[73]	NRT
Fortmann et al 1988[74]	NRT
Gallagher et al 2007[75]	NRT
Garvey et al 2000[76]	NRT
Glavas et al 2003[77]	NRT
Hand et al 2002[78]	NRT
Hanson et al 2003[79]	NRT
Harackiewicz et al 1988[80]	NRT
Herrera et al 1995[81]	NRT
Heydari et al 2012[43]	NRT
Hjalmarson et al 1997[82]	NRT
Hollis et al 2007[83]	NRT
Hotham et al 2006[84]	NRT
Hughes et al 1989[85]	NRT
Hughes et al 1990[86]	NRT
Hughes et al 2003[87]	NRT
Hurt et al 1990[88]	NRT
Hurt et al 1994[89]	NRT
Jamrozik et al 1984[90]	NRT
Jarvis et al 1982[91]	NRT
Jensen et al 1990[92]	NRT
Killen et al 1997[93]	NRT
Killen et al 1999[94]	NRT
Kornitzer et al 1995[95]	NRT

Levin et al 1994[96]	NRT
Lewis et al 1998[97]	NRT
Malcolm et al 1980[98]	NRT
Merz et al 1993[99]	NRT
Molyneux et al 2003[100]	NRT
Moolchan et al 2005[101]	NRT
Murray et al 1996[102]	NRT
Myung et al 2007[103]	NRT
Nilsson et al 1996[104]	NRT
Paoletti et al 1996[105]	NRT
Perng et al 1998[106]	NRT
Piper et al 2007[26]	NRT
Piper et al 2009[27]	NRT
Pollak et al 2007[107]	NRT
Prapavessis et al 2007[108]	NRT
Puska et al 1995[109]	NRT
Rennard et al 2006[110]	NRT
Richmond et al 1994[111]	NRT
Rigotti et al 2009[112]	NRT
Rubinstein et al 2008[113]	NRT
Russell et al 1993[114]	NRT
Sachs et al 1993[115]	NRT
Sadr Azodi et al 2009[116]	NRT
Schauffler et al 2001[117]	NRT

Schneider et al 1983[118]	NRT
Schneider et al 1996[119]	NRT
Schuurmans et al 2004[120]	NRT
Sheng et al 2013[30]	NRT
Shiffman et al 2002[121]	NRT
Smith et al 2003[122]	NRT
Stapleton et al 1995[123]	NRT
Stapleton et al 2011[124]	NRT
Sun et al 2009[125]	NRT
Swanson et al 2003[33]	NRT
Tonnesen et al 1991[126]	NRT
Tonnesen et al 1993[127]	NRT
Tonnesen et al 2000[128]	NRT
Tonnesen et al 2006[129]	NRT
Transdermal Nicotine Study Group et al 1991[130]	NRT
Walker et al 2011[131]	NRT
Warner et al 2005[132]	NRT
Westman et al 1993[133]	NRT
Wisborg et al 2000[134]	NRT
Yudkin et al 2004[135]	NRT

Supplemental Table 2 - Risk-of-bias assessment of randomized controlled trials of nicotine replacement therapy, bupropion, and varenicline included in the analysis of serious adverse cardiovascular events

Author	Year	Treatment	Sequence Generation	Allocation Concealment	Blinding	Use of Placebo	Biological Confirmation of Cessation
AKIA401[136]	1992	Bupropion	Unclear	Unclear	Yes	Yes	Unclear
Covey LS[137]	2007	Bupropion	Yes	Unclear	Yes	Yes	Yes
Dalsgareth OJ[138]	2004	Bupropion	Yes	Unclear	Yes	Yes	Yes
Eisenberg[139]	2013	Bupropion	Yes	Yes	Yes	Yes	Yes
Evins AE[140]	2007	Bupropion	Unclear	Unclear	Yes	Yes	Yes
Fossati R[141]	2007	Bupropion	Yes	Unclear	Yes	Yes	Yes
George TP[142]	2002	Bupropion	Yes	Unclear	Yes	Yes	Yes
Gonzales D[143]	2006	Bupropion	Yes	Yes	Yes	Yes	Yes
Gonzales DH[144]	2001	Bupropion	Yes	Unclear	Yes	Yes	Yes
Hays JT[145]	2001	Bupropion	Yes	Yes	Yes	Yes	Yes
Hurt RD[146]	1997	Bupropion	Unclear	Unclear	Yes	Yes	Yes
Jorenby DE[147]	2006	Bupropion	Yes	Yes	Yes	Yes	Yes
Jorenby DE[148]	1999	Bupropion	Unclear	Unclear	Yes	Yes	Yes
McCarthy DE[149]	2008	Bupropion	Yes	Yes	Yes	Yes	Yes
Muramoto ML[150]	2007	Bupropion	Yes	Yes	Yes	Yes	Yes
Planer D[151]	2011	Bupropion	Unclear	Yes	Yes	Yes	Unclear
Puska PM[152]	2005	Bupropion	Unclear	Unclear	Yes	Yes	Yes
Rigotti NA[153]	2006	Bupropion	Yes	Yes	Yes	Yes	Yes
SMK20001[154]	2000	Bupropion	Unclear	Yes	Yes	Yes	Yes
Tashkin D[155]	2001	Bupropion	Yes	Yes	Yes	Yes	Yes
Tonstad S[156]	2003	Bupropion	Unclear	Unclear	Yes	Yes	Yes
Uyar M[157]	2007	Bupropion	Unclear	Unclear	Unclear	Unclear	Yes
Zellweger J[158]	2005	Bupropion	Unclear	Unclear	Yes	Yes	Yes
ZYB30011[159]	2002	Bupropion	Unclear	Unclear	Yes	Yes	Yes
ZYB40001[160]	2001	Bupropion	Unclear	Unclear	Yes	Yes	Yes
ZYB40005[161]	2001	Bupropion	Unclear	Unclear	Yes	Yes	Yes
ZYB40030[162]	2003	Bupropion	Unclear	Unclear	Yes	Yes	Yes
ZYBAK1A402[163]	1994	Bupropion	Unclear	Unclear	Yes	Yes	Yes
Blondal T[164]	1997	NRT	Yes	Unclear	Yes	Yes	Yes
Etter J[165]	2002	NRT	Yes	Unclear	Yes	Yes	Unclear
Glover ED[166]	2002	NRT	Yes	Unclear	Yes	Yes	Yes
Gourlay SG[167]	1995	NRT	Yes	Unclear	Yes	Yes	Yes
Hays JT[168]	1999	NRT	Yes	Yes	Yes	Yes	Yes
Hjalmarson A[169]	1994	NRT	Unclear	Unclear	Yes	Yes	Yes

Joseph AM[170]	1996	NRT	Yes	Unclear	Yes	Yes	Yes
Oncken C[171]	2007	NRT	Yes	Unclear	Yes	Yes	Yes
Schneider NG[172]	1995	NRT	Unclear	Unclear	Yes	Yes	Yes
Shiffman S[173]	2009	NRT	Yes	Unclear	Yes	Yes	Yes
Sonderskov J[174]	1997	NRT	Unclear	Unclear	Yes	Yes	Unclear
Sutherland G[175]	1992	NRT	Yes	Unclear	Yes	Yes	Yes
Thomsen T[176]	2010	NRT	Yes	Yes	Unclear	Unclear	Yes
Tonnesen P[177]	2012	NRT	Yes	Yes	Yes	Yes	Yes
Tonnesen P[178]	1999	NRT	Yes	Yes	Yes	Yes	Yes
Tonnesen P[179]	1988	NRT	Unclear	Unclear	Unclear	Unclear	Yes
Wallstrom M[180]	2000	NRT	Unclear	Unclear	Yes	Yes	Yes
Wennike P[181]	2003	NRT	Unclear	Unclear	Yes	Yes	Yes
Aubin HJ[182]	2008	Varenicline	Yes	Unclear	Unclear	Yes	Yes
Bolliger C[183]	2010	Varenicline	Yes	Yes	Yes	Yes	Yes
Fagerstrom K[184]	2010	Varenicline	Yes	Yes	Yes	Yes	Yes
Garza D[185]	2011	Varenicline	Yes	Yes	Yes	Yes	Yes
Nakamura M[186]	2007	Varenicline	Yes	Yes	Yes	Yes	Yes
Niaura R[187]	2008	Varenicline	Yes	Yes	Yes	Yes	Yes
Nides M[188]	2006	Varenicline	Yes	Yes	Yes	Yes	Yes
Oncken C[189]	2006	Varenicline	Unclear	Yes	Yes	Yes	Yes
Rennard S[190]	2012	Varenicline	Yes	Yes	Yes	Yes	Yes
Rigotti N[191]	2010	Varenicline	Yes	Yes	Yes	Yes	Yes
Steinberg M[192]	2011	Varenicline	Yes	Yes	Yes	Yes	Yes
Tashkin D[193]	2011	Varenicline	Yes	Yes	Yes	Yes	Yes
Tonnesen P[194]	2013	Varenicline	Yes	Yes	Yes	Yes	Yes
Tonstad S[195]	2006	Varenicline	Yes	Yes	Yes	Yes	Yes
Tsai S[196]	2007	Varenicline	Unclear	Unclear	Yes	Yes	Yes
Williams KE[197]	2007	Varenicline	Unclear	Unclear	Yes	Yes	Yes
Wong J[198]	2012	Varenicline	Yes	Yes	Yes	Yes	Yes

Appendix 3. Retrospective power calculation for detection of harm or protection of harm

We conducted a post-hoc retrospective power calculation to examine our power to detect differences between interventions for MACE. The meta-analysis pooling all control group risks yields pooled proportion of 0.4% (95% confidence interval 0.3% to 0.6%). That is 4 out of 1,000 patients who are attempting to quit smoking, but do not receive any pharmacotherapy to aid smoking cessation, are expected to suffer from a major adverse cardiovascular event (MACE). The uncertainty interval is 3 to 6 patients out of 1,000.

The estimated relative risk for NRT versus control was 1.95, and so, one would expect approximately 8 out of 1,000 patients on NRT will suffer from a MACE.

The estimated relative risk for buproprion was 0.45, and so, one would expect that approximately 2 out of 1,000 patients on buproprion will suffer from a MACE.

The estimated relative risk for varenicline was 1.34, and so, one would expect that approximately 5-6 out of 1,000 patient son varenicline will suffer from a MACE.

The power to demonstrate these expected differences between the considered smoking cessation interventions can be retrospectively estimated using conventional post hoc power calculations for binary outcomes. A retrospective power calculation requires the following inputs:

- The sample size (i.e. number of patients) of the data set
- Some realistic assumption of a control group risk
- Some realistic assumption of an intervention group risk. This can be derived from multiplying the control group with a relative risk.

Below we provide retrospective power estimates based on the assumptions that the control group risk is 0.4%, 0.3%, or 0.6%, and based on the assumptions that the relative risks are exactly that of the primary network meta-analysis results, or other reasonable relative risk estimate assumptions for power calculations. The total number of patients in the network meta-analysis of MACE was 29,413.

For varenicline, the RR is relatively small, and thus, the retrospective power to demonstrate harm is low. However, the retrospective power to demonstrate non-inferiority to upper harm limits is considerable. For example, the power to demonstrate that varenicline causes no more harm than what corresponds to a RR of 1.95 (i.e., the NRT RR) is 95%. By the same token, the power of buproprion to demonstrate superiority (protective effect) to both varenicline and NRT is higher than the power to demonstrate superiority to control.

Retrospective power calculation to demonstrate harm for NRT

Assumed control risk	Assumed relative risk		
	RR=1.75	**RR=1.95**	**RR=2.50**
P_C=0.3%	85.3%	95.7%	99.99%
P_C=0.4%	93.6%	98.9%	99.99%
P_C=0.6%	98.9%	99.9%	99.99%

Retrospective power calculation to demonstrate harm for Varenicline

Assumed control risk	Assumed relative risk		
	RR=1.25	**RR=1.34**	**RR=1.50**
P_C=0.3%	19.7%	31.4%	55.7%
P_C=0.4%	24.6%	40.1%	68.1%
P_C=0.6%	34.9%	55.4%	84.7%

Retrospective power calculation to demonstrate non-inferiority of Varenicline vs NRT (the Varenicline RR was assumed to be 1.34)

Assumed control risk	Assumed NRT relative risk		
	RR=1.75	**RR=1.95**	**RR=2.50**
P_C=0.3%	93.7%	98.9%	99.99%
P_C=0.4%	98.1%	99.9%	99.99%
P_C=0.6%	99.9%	99.99%	99.99%

Retrospective power calculation to demonstrate protective effect of buproprion

Assumed control risk	Assumed relative risk		
	RR=0.60	**RR=0.45**	**RR=0.30**
P_C=0.3%	55.7%	85.9%	98.3%
P_C=0.4%	68.1%	93.9%	99.7%
P_C=0.6%	84.6%	99.0%	99.9%

Supplemental References:

1. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in medicine. 2004;23:3105-3124.
2. Thorlund K, Thabane L, Mills EJ. Modelling Heterogeneity Variances in Multiple Treatment Comparison Meta-Analysis -- Are Informative Priors the Better Solution? BMC Med Res Meth. 2013;13.
3. Turner RM, Davey J, Clarke MJ, Thomspn SG, Higgins J. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. . International journal of epidemiology. 2012;41:818-827.
4. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50:683-691.
5. Walter SD. Choice of effect measure for epidemiological data. Journal of clinical epidemiology. 2000;53:931-939.
6. Ahluwalia JS, McNagny SE, Clark WS. Smoking cessation among inner-city African Americans using the nicotine transdermal patch. J Gen Intern Med. 1998;13:1-8.
7. GlaxoSmithKline. AK1A4010: A Parallel, Randomized, Double-Blind, Placebo-Controlled, 1-Year Pilot Study of the Effects of ZYBAN† (Bupropion Hydrochloride Sustained Release Tablets) as an Aid to Smoking Cessation in Adult Cigarette Smokers Who are Not Motivated to Quit Smoking2000.

8. 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. Addiction. 2004;99:1206-1218.

9. Brown RA, Niaura R, Lloyd-Richardson EE, Strong DR, Kahler CW, Abrantes AM, Abrams D, Miller IW. Bupropion and cognitive-behavioral treatment for depression in smoking cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2007;9:721-730.

10. Cox LS, Nollen NL, Mayo MS, Choi WS, Faseru B, Benowitz NL, Tyndale RF, Okuyemi KS, Ahluwalia JS. Bupropion for smoking cessation in African American light smokers: a randomized controlled trial. Journal of the National Cancer Institute. 2012;104:290-298.

11. 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. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2001;3:397-403.

12. Evins AE, Cather C, Deckersbach T, Freudenreich O, Culhane MA, Olm-Shipman CM, Henderson DC, Schoenfeld DA, Goff DC, Rigotti NA. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. J Clin Psychopharmacol. 2005;25:218-225.

13. George TP, Vessicchio JC, Sacco KA, Weinberger AH, Dudas MM, Allen TM, Creeden CL, Potenza MN, Feingold A, Jatlow PI. A placebo-controlled trial of

bupropion combined with nicotine patch for smoking cessation in schizophrenia. Biol Psychiatry. 2008;63:1092-1096.

14. Grant KM, Kelley SS, Smith LM, Agrawal S, Meyer JR, Romberger DJ. Bupropion and nicotine patch as smoking cessation aids in alcoholics. Alcohol. 2007;41:381-391.

15. Haggstram FM, Chatkin JM, Sussenbach-Vaz E, Cesari DH, Fam CF, Fritscher CC. A controlled trial of nortriptyline, sustained-release bupropion and placebo for smoking cessation: preliminary results. Pulm Pharmacol Ther. 2006;19:205-209.

16. Hall SM, Humfleet GL, Reus VI, Munoz RF, Hartz DT, Maude-Griffin R. Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psychiatry. 2002;59:930-936.

17. Hatsukami DK, Rennard S, Patel MK, Kotlyar M, Malcolm R, Nides MA, Dozier G, Bars MP, Jamerson BD. Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking. The American journal of medicine. 2004;116:151-157.

18. Hertzberg MA, Moore SD, Feldman ME, Beckham JC. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. J Clin Psychopharmacol. 2001;21:94-98.

19. Holt S, Timu-Parata C, Ryder-Lewis S, Weatherall M, Beasley R. Efficacy of bupropion in the indigenous Maori population in New Zealand. Thorax. 2005;60:120-123.

20. Hurt RD, Krook JE, Croghan IT, Loprinzi CL, Sloan JA, Novotny PJ, Kardinal CG, Knost JA, Tirona MT, Addo F, Morton RF, Michalak JC, Schaefer PL, Porter PA, Stella PJ. Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. J Clin Oncol. 2003;21:914-920.

21. Karam-Hage M, Strobbe S, Robinson JD, Brower KJ. Bupropion-SR for smoking cessation in early recovery from alcohol dependence: a placebo-controlled, double-blind pilot study. The American journal of drug and alcohol abuse. 2011;37:487-490.

22. Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, Stone C, Samuels D, Levin SK, Green S, Schatzberg AF. Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. J Consult Clin Psychol. 2004;72:729-735.

23. Killen JD, Fortmann SP, Murphy GM, Jr., Hayward C, Arredondo C, Cromp D, Celio M, Abe L, Wang Y, Schatzberg AF. Extended treatment with bupropion SR for cigarette smoking cessation. J Consult Clin Psychol. 2006;74:286-294.

24. Lerman C, Roth D, Kaufmann V, Audrain J, Hawk L, Liu A, Niaura R, Epstein L. Mediating mechanisms for the impact of bupropion in smoking cessation treatment. Drug Alcohol Depend. 2002;67:219-223.

25. Myles PS, Leslie K, Angliss M, Mezzavia P, Lee L. Effectiveness of bupropion as an aid to stopping smoking before elective surgery: a randomised controlled trial. Anaesthesia. 2004;59:1053-1058.

26. Piper ME, Federman EB, McCarthy DE, Bolt DM, Smith SS, Fiore MC, Baker TB. Efficacy of bupropion alone and in combination with nicotine gum. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2007;9:947-954.

27. Piper ME, Smith SS, Schlam TR, Fiore MC, Jorenby DE, Fraser D, Baker TB. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch Gen Psychiatry. 2009;66:1253-1262.

28. Schmitz JM, Stotts AL, Mooney ME, Delaune KA, Moeller GF. Bupropion and cognitive-behavioral therapy for smoking cessation in women. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2007;9:699-709.

29. Schnoll RA, Martinez E, Tatum KL, Weber DM, Kuzla N, Glass M, Ridge JA, Langer C, Miyamoto C, Wileyto EP, Leone F. A bupropion smoking cessation clinical trial for cancer patients. Cancer causes & control : CCC. 2010;21:811-820.

30. Sheng LX, Tang YL, Jiang ZN, Yao CH, Gao JY, Xu GZ, Tong XY. Sustained-release bupropion for smoking cessation in a Chinese sample: A double-blind, placebo-controlled randomized trial. Nicotine and Tobacco Research. 2013;15:320-325.

31. Simon JA, Duncan C, Carmody TP, Hudes ES. Bupropion for smoking cessation: a randomized trial. Arch Intern Med. 2004;164:1797-1803.

32. Simon JA, Duncan C, Huggins J, Solkowitz S, Carmody TP. Sustained-release bupropion for hospital-based smoking cessation: a randomized trial. Nicotine

& tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2009;11:663-669.

33. Swanson NA, Burroughs CC, Long MA, Lee RW. Controlled trial for smoking cessation in a Navy shipboard population using nicotine patch, sustained-release buproprion, or both. Mil Med. 2003;168:830-834.

34. Tonnesen P, Tonstad S, Hjalmarson A, Lebargy F, Van Spiegel PI, Hider A, Sweet R, Townsend J. A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. J Intern Med. 2003;254:184-192.

35. 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. Arch Intern Med. 2005;165:2286-2292.

36. Weiner E, Ball MP, Buchholz AS, Gold JM, Evins AE, McMahon RP, Buchanan RW. Bupropion sustained release added to group support for smoking cessation in schizophrenia: a new randomized trial and a meta-analysis. The Journal of clinical psychiatry. 2012;73:95-102.

37. Wittchen HU, Hoch E, Klotsche J, Muehlig S. Smoking cessation in primary care - a randomized controlled trial of bupropione, nicotine replacements, CBT and a minimal intervention. International journal of methods in psychiatric research. 2011;20:28-39.

38. Zernig G, Wallner R, Grohs U, Kriechbaum N, Kemmler G, Saria A. A randomized trial of short psychotherapy versus sustained-release bupropion for smoking cessation. Addiction. 2008;103:2024-2031.

39. GlaxoSmithKline. ZYBF4001: Evaluation of efficacy of safety of ZybanTM (bupropion hydrochloride extended release tablet) in smoking cessation aid in nicotine-dependent patients. Multicentre, randomized, double blind, placebo-controlled study, 6 months length.2002.

40. de Dios MA, Anderson BJ, Stanton C, Audet DA, Stein M. Project Impact: A pharmacotherapy pilot trial investigating the abstinence and treatment adherence of Latino light smokers. Journal of Substance Abuse Treatment. 2012;43:322-330.

41. Ebbert JO, Croghan IT, Severson HH, Schroeder DR, Hays JT. A pilot study of the efficacy of varenicline for the treatment of smokeless tobacco users in Midwestern United States. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2011;13:820-826.

42. Ferketich AK, Diaz P, Browning KK, Lu B, Koletar SL, Reynolds NR, Wewers ME. Safety of varenicline among smokers enrolled in the lung HIV study. Nicotine and Tobacco Research. 2013;15:247-254.

43. Heydari G, Talischi F, Tafti SF, Masjedi MR. Quitting smoking with varenicline: parallel, randomised efficacy trial in Iran. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16:268-272.

44. Hong LE, Thaker GK, McMahon RP, Summerfelt A, Rachbeisel J, Fuller RL, Wonodi I, Buchanan RW, Myers C, Heishman SJ, Yang J, Nye A. Effects of moderate-dose treatment with varenicline on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 2011;68:1195-1206.

45. Hughes JR, Rennard SI, Fingar JR, Talbot SK, Callas PW, Fagerstrom KO. Efficacy of varenicline to prompt quit attempts in smokers not currently trying to quit: a randomized placebo-controlled trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2011;13:955-964.

46. Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL. Varenicline decreases alcohol consumption in heavy-drinking smokers. Psychopharmacology. 2012;223:299-306.

47. Poling J, Rounsaville B, Gonsai K, Severino K, Sofuoglu M. The safety and efficacy of varenicline in cocaine using smokers maintained on methadone: a pilot study. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2010;19:401-408.

48. Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, George TP. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. The Journal of clinical psychiatry. 2012;73:654-660.

49. Tsukahara H, Noda K, Saku K. A randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers: efficacy, safety and withdrawal symptoms (the VN-SEESAW study). Circ J. 2010;74:771-778.

50. Wang C, Xiao D, Chan KP, Pothirat C, Garza D, Davies S. Varenicline for smoking cessation: a placebo-controlled, randomized study. Respirology. 2009;14:384-392.

51. Abelin T, Ehrsam R, Buhler-Reichert A, Imhof PR, Muller P, Thommen A, Vesanen K. Effectiveness of a transdermal nicotine system in smoking cessation studies. Methods Find Exp Clin Pharmacol. 1989;11:205-214.

52. Areechon W, Punnotok J. Smoking cessation through the use of nicotine chewing gum: a double-blind trial in Thailand. Clinical therapeutics. 1988;10:183-186.

53. 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. Clin Pharmacol Ther. 2005;78:689-696.

54. Blondal T. Controlled trial of nicotine polacrilex gum with supportive measures. Arch Intern Med. 1989;149:1818-1821.

55. Blondal T, Gudmundsson LJ, Olafsdottir I, Gustavsson G, Westin A. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. Bmj. 1999;318:285-288.

56. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a

randomized, double-blind, placebo-controlled trial. Arch Intern Med. 2000;160:3128-3134.

57. Bolliger CT, Zellweger JP, Danielsson T, van Biljon X, Robidou A, Westin A, Perruchoud AP, Sawe U. Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. Bmj. 2000;321:329-333.

58. Comparison of four methods of smoking withdrawal in patients with smoking related diseases. Report by a subcommittee of the Research Committee of the British Thoracic Society. British medical journal. 1983;286:595-597.

59. Buchkremer G, Bents H, Minneker E, Opitz K. [Long-term effects of a combination of transdermal nicotine administration with behavior therapy for smoking cessation]. Der Nervenarzt. 1988;59:488-490.

60. Campbell IA, Prescott RJ, Tjeder-Burton SM. Smoking cessation in hospital patients given repeated advice plus nicotine or placebo chewing gum. Respiratory medicine. 1991;85:155-157.

61. Campbell IA, Prescott RJ, Tjeder-Burton SM. Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study. Respiratory medicine. 1996;90:47-51.

62. Chou KR, Chen R, Lee JF, Ku CH, Lu RB. The effectiveness of nicotine-patch therapy for smoking cessation in patients with schizophrenia. Int J Nurs Stud. 2004;41:321-330.

63. 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. J Consult Clin Psychol. 1996;64:314-323.

64. Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, Lewis S, Smoking N, Pregnancy Trial T. A randomized trial of nicotine-replacement therapy patches in pregnancy. The New England journal of medicine. 2012;366:808-818.

65. Cooney NL, Cooney JL, Perry BL, Carbone M, Cohen EH, Steinberg HR, Pilkey DT, Sevarino K, Oncken CA, Litt MD. Smoking cessation during alcohol treatment: a randomized trial of combination nicotine patch plus nicotine gum. Addiction. 2009;104:1588-1596.

66. Croghan GA, Sloan JA, Croghan IT, Novotny P, Hurt RD, DeKrey WL, Mailliard JA, Ebbert LP, Swan DK, Walsh DJ, Wiesenfeld M, Levitt R, Stella P, Johnson PA, Tschetter LK, Loprinzi C. 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. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2003;5:181-187.

67. Dale LC, Hurt RD, Offord KP, Lawson GM, Croghan IT, Schroeder DR. High-dose nicotine patch therapy. Percentage of replacement and smoking cessation. Jama. 1995;274:1353-1358.

68. Daughton DM, Heatley SA, Prendergast JJ, Causey D, Knowles M, Rolf CN, Cheney RA, Hatlelid K, Thompson AB, Rennard SI. Effect of transdermal

nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. Arch Intern Med. 1991;151:749-752.

69. Daughton D, Susman J, Sitorius M, Belenky S, Millatmal T, Nowak R, Patil K, Rennard SI. Transdermal nicotine therapy and primary care. Importance of counseling, demographic, and participant selection factors on 1-year quit rates. The Nebraska Primary Practice Smoking Cessation Trial Group. Arch Fam Med. 1998;7:425-430.

70. Daughton DM, Fortmann SP, Glover ED, Hatsukami DK, Heatley SA, Lichtenstein E, Repsher L, Millatmal T, Killen JD, Nowak RT, Ullrich F, Patil KD, Rennard SI. The smoking cessation efficacy of varying doses of nicotine patch delivery systems 4 to 5 years post-quit day. Prev Med. 1999;28:113-118.

71. Davidson M, Epstein M, Burt R, Schaefer C, Whitworth G, McDonald A. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. Arch Fam Med. 1998;7:569-574.

72. Fagerstrom KO. A comparison of psychological and pharmacological treatment in smoking cessation. Journal of behavioral medicine. 1982;5:343-351.

73. Fiore MC, Kenford SL, Jorenby DE, Wetter DW, Smith SS, Baker TB. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. Chest. 1994;105:524-533.

74. Fortmann SP, Killen JD, Telch MJ, Newman B. Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford Stop Smoking Project. Jama. 1988;260:1575-1580.

75. Gallagher SM, Penn PE, Schindler E, Layne W. A comparison of smoking cessation treatments for persons with schizophrenia and other serious mental illnesses. J Psychoactive Drugs. 2007;39:487-497.

76. Garvey AJ, Kinnunen T, Nordstrom BL, Utman CH, Doherty K, Rosner B, Vokonas PS. Effects of nicotine gum dose by level of nicotine dependence. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2000;2:53-63.

77. Glavas D, Rumboldt M, Rumboldt Z. Smoking cessation with nicotine replacement therapy among health care workers: randomized double-blind study. Croat Med J. 2003;44:219-224.

78. Hand S, Edwards S, Campbell IA, Cannings R. Controlled trial of three weeks nicotine replacement treatment in hospital patients also given advice and support. Thorax. 2002;57:715-718.

79. Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2003;5:515-526.

80. Harackiewicz JM, Blair LW, Sansone C, Epstein JA, Stuchell RN. Nicotine gum and self-help manuals in smoking cessation: an evaluation in a medical context. Addict Behav. 1988;13:319-330.

81. Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerstrom KO. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. Chest. 1995;108:447-451.

82. Hjalmarson A, Nilsson F, Sjostrom L, Wiklund O. The nicotine inhaler in smoking cessation. Arch Intern Med. 1997;157:1721-1728.

83. Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. Tob Control. 2007;16 Suppl 1:i53-59.

84. Hotham ED, Gilbert AL, Atkinson ER. A randomised-controlled pilot study using nicotine patches with pregnant women. Addict Behav. 2006;31:641-648.

85. Hughes JR. Dependence potential and abuse liability of nicotine replacement therapies. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 1989;43:11-17.

86. Hughes JR, Gust SW, Keenan RM, Fenwick JW. Effect of dose on nicotine's reinforcing, withdrawal-suppression and self-reported effects. The Journal of pharmacology and experimental therapeutics. 1990;252:1175-1183.

87. Hughes JR, Novy P, Hatsukami DK, Jensen J, Callas PW. Efficacy of nicotine patch in smokers with a history of alcoholism. Alcohol Clin Exp Res. 2003;27:946-954.

88. Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine-replacement therapy with use of a transdermal nicotine patch--a randomized double-blind placebo-controlled trial. Mayo Clin Proc. 1990;65:1529-1537.

89. Hurt RD, Dale LC, Fredrickson PA, Caldwell CC, Lee GA, Offord KP, Lauger GG, Marusic Z, Neese LW, Lundberg TG. Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up. One-year outcome and percentage of nicotine replacement. Jama. 1994;271:595-600.

90. Jamrozik K, Fowler G, Vessey M, Wald N. Placebo controlled trial of nicotine chewing gum in general practice. British medical journal. 1984;289:794-797.

91. Jarvis MJ, Raw M, Russell MA, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. British medical journal. 1982;285:537-540.

92. Jensen EJ, Schmidt E, Pedersen B, Dahl R. Effect of nicotine, silver acetate, and ordinary chewing gum in combination with group counselling on smoking cessation. Thorax. 1990;45:831-834.

93. Killen JD, Fortmann SP, Davis L, Varady A. Nicotine patch and self-help video for cigarette smoking cessation. J Consult Clin Psychol. 1997;65:663-672.

94. Killen JD, Fortmann SP, Davis L, Strausberg L, Varady A. Do heavy smokers benefit from higher dose nicotine patch therapy? Exp Clin Psychopharmacol. 1999;7:226-233.

95. Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. Prev Med. 1995;24:41-47.

96. Levin ED, Westman EC, Stein RM, Carnahan E, Sanchez M, Herman S, Behm FM, Rose JE. Nicotine skin patch treatment increases abstinence, decreases withdrawal symptoms, and attenuates rewarding effects of smoking. J Clin Psychopharmacol. 1994;14:41-49.

97. Lewis SF, Piasecki TM, Fiore MC, Anderson JE, Baker TB. Transdermal nicotine replacement for hospitalized patients: a randomized clinical trial. Prev Med. 1998;27:296-303.

98. Malcolm RE, Sillett RW, Turner JA, Ball KP. The use of nicotine chewing gum as an aid to stopping smoking. Psychopharmacology (Berl). 1980;70:295-296.

99. Merz PG, Keller-Stanislawski B, Huber T, Woodcock BG, Rietbrock N. Transdermal nicotine in smoking cessation and involvement of non-specific influences. Int J Clin Pharmacol Ther Toxicol. 1993;31:476-482.

100. Molyneux A, Lewis S, Leivers U, Anderton A, Antoniak M, Brackenridge A, Nilsson F, McNeill A, West R, Moxham J, Britton J. Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. Thorax. 2003;58:484-488.

101. Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, Schroeder JR. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics. 2005;115:e407-414.

102. Murray RP, Bailey WC, Daniels K, Bjornson WM, Kurnow K, Connett JE, Nides MA, Kiley JP. Safety of nicotine polacrilex gum used by 3,094 participants in

the Lung Health Study. Lung Health Study Research Group. Chest. 1996;109:438-445.

103. Myung SK, Seo HG, Park S, Kim Y, Kim DJ, Lee do H, Seong MW, Nam MH, Oh SW, Kim JA, Kim MY. Sociodemographic and smoking behavioral predictors associated with smoking cessation according to follow-up periods: a randomized, double-blind, placebo-controlled trial of transdermal nicotine patches. J Korean Med Sci. 2007;22:1065-1070.

104. Nilsson P, Lundgren H, Soderstrom M, Fagerstrom KO, Nilsson-Ehle P. Effects of smoking cessation on insulin and cardiovascular risk factors--a controlled study of 4 months' duration. J Intern Med. 1996;240:189-194.

105. Paoletti P, Fornai E, Maggiorelli F, Puntoni R, Viegi G, Carrozzi L, Corlando A, Gustavsson G, Sawe U, Giuntini C. Importance of baseline cotinine plasma values in smoking cessation: results from a double-blind study with nicotine patch. Eur Respir J. 1996;9:643-651.

106. Perng RP, Hsieh WC, Chen YM, Lu CC, Chiang SJ. Randomized, double-blind, placebo-controlled study of transdermal nicotine patch for smoking cessation. J Formos Med Assoc. 1998;97:547-551.

107. Pollak KI, Oncken CA, Lipkus IM, Lyna P, Swamy GK, Pletsch PK, Peterson BL, Heine RP, Brouwer RJ, Fish L, Myers ER. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. Am J Prev Med. 2007;33:297-305.

108. Prapavessis H, Cameron L, Baldi JC, Robinson S, Borrie K, Harper T, Grove JR. The effects of exercise and nicotine replacement therapy on smoking rates in women. Addict Behav. 2007;32:1416-1432.

109. Puska P KH, Vartiainen E, Urjanheimo E. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. Tabacco Control. 1995;4:231-235.

110. Rennard SI, Glover ED, Leischow S, Daughton DM, Glover PN, Muramoto M, Franzon M, Danielsson T, Landfeldt B, Westin A. Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2006;8:555-564.

111. Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. Med J Aust. 1994;161:130-135.

112. Rigotti NA, Gonzales D, Dale LC, Lawrence D, Chang Y. A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. Addiction. 2009;104:266-276.

113. Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB. A randomized trial of nicotine nasal spray in adolescent smokers. Pediatrics. 2008;122:e595-600.

114. Russell MA, Stapleton JA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, Connor P. Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. Bmj. 1993;306:1308-1312.

115. Sachs DP, Sawe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. Arch Intern Med. 1993;153:1881-1890.

116. Sadr Azodi O, Lindstrom D, Adami J, Tonnesen H, Nasell H, Gilljam H, Wladis A. The efficacy of a smoking cessation programme in patients undergoing elective surgery: a randomised clinical trial. Anaesthesia. 2009;64:259-265.

117. Schauffler HH, McMenamin S, Olson K, Boyce-Smith G, Rideout JA, Kamil J. Variations in treatment benefits influence smoking cessation: results of a randomised controlled trial. Tob Control. 2001;10:175-180.

118. Schneider NG, Jarvik ME, Forsythe AB, Read LL, Elliott ML, Schweiger A. Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. Addict Behav. 1983;8:253-261.

119. Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. Addiction. 1996;91:1293-1306.

120. Schuurmans MM, Diacon AH, van Biljon X, Bolliger CT. Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: a randomized controlled trial. Addiction. 2004;99:634-640.

121. Shiffman S, Gorsline J, Gorodetzky CW. Efficacy of over-the-counter nicotine patch. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2002;4:477-483.

122. Smith SS, Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Jamerson B, Fiore MC, Baker TB. Targeting smokers at increased risk for relapse: treating women and those with a history of depression. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2003;5:99-109.

123. Stapleton JA, Russell MA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, Wiseman D. Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. Addiction. 1995;90:31-42.

124. Stapleton JA, Sutherland G. Treating heavy smokers in primary care with the nicotine nasal spray: randomized placebo-controlled trial. Addiction. 2011;106:824-832.

125. Sun HQ, Guo S, Chen DF, Jiang ZN, Liu Y, Di XL, Yang FD, Zhang XY, Kosten TR, Lu L. Family support and employment as predictors of smoking cessation success: a randomized, double-blind, placebo-controlled trial of nicotine sublingual tablets in chinese smokers. The American journal of drug and alcohol abuse. 2009;35:183-188.

126. Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. N Engl J Med. 1991;325:311-315.

127. Tonnesen P, Norregaard J, Mikkelsen K, Jorgensen S, Nilsson F. A double-blind trial of a nicotine inhaler for smoking cessation. Jama. 1993;269:1268-1271.

128. Tonnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. Eur Respir J. 2000;16:717-722.

129. Tonnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. Chest. 2006;130:334-342.

130. Transdermal nicotine for smoking cessation. Six-month results from two multicenter controlled clinical trials. Transdermal Nicotine Study Group. Jama. 1991;266:3133-3138.

131. Walker N, Howe C, Bullen C, Grigg M, Glover M, McRobbie H, Laugesen M, Jiang J, Chen MH, Whittaker R, Rodgers A. Does improved access and greater choice of nicotine replacement therapy affect smoking cessation success? Findings from a randomized controlled trial. Addiction. 2011;106:1176-1185.

132. Warner DO, Patten CA, Ames SC, Offord KP, Schroeder DR. Effect of nicotine replacement therapy on stress and smoking behavior in surgical patients. Anesthesiology. 2005;102:1138-1146.

133. Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation. A randomized trial with telephone counseling. Arch Intern Med. 1993;153:1917-1923.

134. Wisborg K, Henriksen, TB, Jespersen, LB, Secher, NJ. Nicotine patches for pregnant smokers: A randomized controlled study. Obstet Gynecol. 2000;96:967-971.

135. Yudkin P, Munafo M, Hey K, Roberts S, Welch S, Johnstone E, Murphy M, Griffiths S, Walton R. Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial. Bmj. 2004;328:989-990.

136. AKIA401:A single-center evaluation of Wellbutrin (bupropion hydrochloride) versus placebo as an aid to smoking cessation in heavy smokers (study 401) 1992.

137. Covey LS, Glassman AH, Jiang H, Fried J, Masmela J, LoDuca C, Petkova E, Rodriguez K. A randomized trial of bupropion and/or nicotine gum as maintenance treatment for preventing smoking relapse. Addiction. 2007;102:1292-1302.

138. Dalsgareth OJ, Hansen NC, Soes-Petersen U, Evald T, Hoegholm A, Barber J, Vestbo J. A multicenter, randomized, double-blind, placebo-controlled, 6-month trial of bupropion hydrochloride sustained-release tablets as an aid to smoking cessation in hospital employees. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2004;6:55-61.

139. Eisenberg MJ, Grandi SM, Gervais A, O'Loughlin J, Paradis G, Rinfret S, Sarrafzadegan N, Sharma S, Lauzon C, Yadav R, Pilote L, Investigators Z. Bupropion for smoking cessation in patients hospitalized with acute myocardial infarction: a randomized, placebo-controlled trial. J Am Coll Cardiol. 2013;61:524-532.

140. Evins AE, Cather C, Culhane MA, Birnbaum A, Horowitz J, Hsieh E, Freudenreich O, Henderson DC, Schoenfeld DA, Rigotti NA, Goff DC. 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. J Clin Psychopharmacol. 2007;27:380-386.

141. Fossati R, Apolone G, Negri E, Compagnoni A, La Vecchia C, Mangano S, Clivio L, Garattini S. A double-blind, placebo-controlled, randomized trial of bupropion for smoking cessation in primary care. Arch Intern Med. 2007;167:1791-1797.

142. George TP, Vessicchio JC, Termine A, Bregartner TA, Feingold A, Rounsaville BJ, Kosten TR. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. Biol Psychiatry. 2002;52:53-61.

143. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. Jama. 2006;296:47-55.

144. Gonzales DH, Nides MA, Ferry LH, Kustra RP, Jamerson BD, Segall N, Herrero LA, Krishen A, Sweeney A, Buaron K, Metz A. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. Clin Pharmacol Ther. 2001;69:438-444.

145. Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, Sachs DP, Wolter TD, Buist AS, Johnston JA, White JD. Sustained-release bupropion for

pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. Ann Intern Med. 2001;135:423-433.

146. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, Croghan IT, Sullivan PM. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med. 1997;337:1195-1202.

147. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. Jama. 2006;296:56-63.

148. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999;340:685-691.

149. McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Fiore MC, Baker TB. A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2008;10:717-729.

150. 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. Arch Pediatr Adolesc Med. 2007;161:1068-1074.

151. Planer D, Lev I, Elitzur Y, Sharon N, Ouzan E, Pugatsch T, Chasid M, Rom M, Lotan C. Bupropion for smoking cessation in patients with acute coronary syndrome. Arch Intern Med. 2011;171:1055-1060.

152. Puska PM, Barrueco M, Roussos C, Hider A, Hogue S. The participation of health professionals in a smoking-cessation programme positively influences the smoking cessation advice given to patients. Int J Clin Pract. 2005;59:447-452.

153. Rigotti NA, Thorndike AN, Regan S, McKool K, Pasternak RC, Chang Y, Swartz S, Torres-Finnerty N, Emmons KM, Singer DE. Bupropion for smokers hospitalized with acute cardiovascular disease. The American journal of medicine. 2006;119:1080-1087.

154. SMK20001:A Multi-Center, Double-Blind, Double-Dummy, Placebo-Controlled, Randomized, Parallel Group, Dose Response Evaluation of a New Chemical Entity (NCE) and ZYBAN (bupropion hydrochloride) Sustained Release (300mg/day) versus Placebo As Aids to Smoking Cessation 2000.

155. Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, Gonzales D, Dozier G, Patel MK, Jamerson B. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet. 2001;357:1571-1575.

156. Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, Silagy C, van Spiegel PI, Astbury C, Hider A, Sweet R. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J. 2003;24:946-955.

157. Uyar M, Filiz A, Bayram N, Elbek O, Herken H, Topcu A, Dikensoy O, Ekinci E. A randomized trial of smoking cessation. Medication versus motivation. Saudi medical journal. 2007;28:922-926.

158. Zellweger JP, Boelcskei PL, Carrozzi L, Sepper R, Sweet R, Hider AZ. Bupropion SR vs placebo for smoking cessation in health care professionals. Am J Health Behav. 2005;29:240-249.

159. ZYB 30011:A multicentre, randomised, double- blind, placebo controlled study to evaluate the efficacy and tolerability of bupropion hydrochloride (SR) sustained release (2 x 150mg per day) versus placebo as an aid to smoking cessation in smokers with at least one cardiovascular (CV) risk factor

2002.

160. ZYB40001:A randomized, double-blind, placebo-controlled, 12-week smoking cessation trial of Zyban (150 mg bid) in adult smokers previously treated with Zyban2001.

161. ZYB40005:The effect of sustained-release bupropion HCl vs. placebo as an aid to smoking reduction leading to cessation among smokers unwilling and unable to quit smoking

2001.

162. ZYB400030:A Multi-centre, Randomised, Double-Blind, Placebo controlled study to evaluate the efficacy and tolerability of bupropion hydrochloride (SR) sustained release versus placebo as an aid to smoking cessation in a population of smokers with Chronic Obstructive Pulmonary Disease 2003.

163. ZYBAKIA402:A single center evaluation of Wellbutrin (bupropion hydrochloride) versus placebo as an aid to smoking cessation (study 402) 1994.

164. Blondal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. Eur Respir J. 1997;10:1585-1590.

165. Etter JF, Laszlo E, Zellweger JP, Perrot C, Perneger TV. Nicotine replacement to reduce cigarette consumption in smokers who are unwilling to quit: a randomized trial. J Clin Psychopharmacol. 2002;22:487-495.

166. Glover ED, Glover PN, Franzon M, Sullivan CR, Cerullo CC, Howell RM, Keyes GG, Nilsson F, Hobbs GR. A comparison of a nicotine sublingual tablet and placebo for smoking cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2002;4:441-450.

167. Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. Bmj. 1995;311:363-366.

168. Hays JT, Croghan IT, Schroeder DR, Offord KP, Hurt RD, Wolter TD, Nides MA, Davidson M. Over-the-counter nicotine patch therapy for smoking cessation:

results from randomized, double-blind, placebo-controlled, and open label trials. Am J Public Health. 1999;89:1701-1707.

169. Hjalmarson A, Franzon M, Westin A, Wiklund O. Effect of nicotine nasal spray on smoking cessation. A randomized, placebo-controlled, double-blind study. Arch Intern Med. 1994;154:2567-2572.

170. Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, Sherman SE, Cleveland M, Antonuccio DO, Hartman N, McGovern PG. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med. 1996;335:1792-1798.

171. Oncken C, Cooney J, Feinn R, Lando H, Kranzler HR. Transdermal nicotine for smoking cessation in postmenopausal women. Addict Behav. 2007;32:296-309.

172. Schneider NG, Olmstead R, Mody FV, Doan K, Franzon M, Jarvik ME, Steinberg C. Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. Addiction. 1995;90:1671-1682.

173. Shiffman S, Ferguson SG, Strahs KR. Quitting by gradual smoking reduction using nicotine gum: a randomized controlled trial. Am J Prev Med. 2009;36:96-104 e101.

174. Sonderskov J, Olsen J, Sabroe S, Meillier L, Overvad K. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. Am J Epidemiol. 1997;145:309-318.

175. Sutherland G, Stapleton JA, Russell MA, Jarvis MJ, Hajek P, Belcher M, Feyerabend C. Randomised controlled trial of nasal nicotine spray in smoking cessation. Lancet. 1992;340:324-329.

176. Thomsen T, Tonnesen H, Okholm M, Kroman N, Maibom A, Sauerberg ML, Moller AM. Brief smoking cessation intervention in relation to breast cancer surgery: a randomized controlled trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2010;12:1118-1124.

177. Tonnesen P, Lauri H, Perfekt R, Mann K, Batra A. Efficacy of a nicotine mouth spray in smoking cessation: A randomised, double-blind trial. European Respiratory Journal. 2012;40:548-554.

178. Tonnesen P, Paoletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, Rijcken B, Sawe U. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. Eur Respir J. 1999;13:238-246.

179. Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnersen AB, Forchammer H, Stockner M. Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. N Engl J Med. 1988;318:15-18.

180. Wallstrom M, Nilsson F, Hirsch JM. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. Addiction. 2000;95:1161-1171.

181. Wennike P, Danielsson T, Landfeldt B, Westin A, Tonnesen P. Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. Addiction. 2003;98:1395-1402.

182. Aubin HJ, Bobak A, Britton JR, Oncken C, Billing CB, Jr., Gong J, Williams KE, Reeves KR. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax. 2008;63:717-724.

183. Bolliger CT, Issa JS, Posadas-Valay R, Safwat T, Abreu P, Correia EA, Park PW, Chopra P. Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. Clinical therapeutics. 2011;33:465-477.

184. Fagerstrom K, Gilljam H, Metcalfe M, Tonstad S, Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. Bmj. 2010;341:c6549.

185. Garza D, Murphy M, Tseng LJ, Riordan HJ, Chatterjee A. A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo. Biol Psychiatry. 2011;69:1075-1082.

186. Nakamura M, Oshima A, Fujimoto Y, Maruyama N, Ishibashi T, Reeves KR. Efficacy and tolerability of varenicline, an alpha4beta2 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. Clinical therapeutics. 2007;29:1040-1056.

187. Niaura R, Hays JT, Jorenby DE, Leone FT, Pappas JE, Reeves KR, Williams KE, Billing CB, Jr. The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial. Curr Med Res Opin. 2008;24:1931-1941.

188. Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, Reeves KR. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Arch Intern Med. 2006;166:1561-1568.

189. Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, Anziano R, Reeves K. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med. 2006;166:1571-1577.

190. Rennard S, Hughes J, Cinciripini PM, Kralikova E, Raupach T, Arteaga C, St Aubin LB, Russ C, Flexible Quit Date Study G. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012;14:343-350.

191. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation. 2010;121:221-229.

192. Steinberg MB, Randall J, Greenhaus S, Schmelzer AC, Richardson DL, Carson JL. Tobacco dependence treatment for hospitalized smokers: a randomized, controlled, pilot trial using varenicline. Addict Behav. 2011;36:1127-1132.

193. Tashkin DP, Rennard S, Hays JT, Ma W, Lawrence D, Lee TC. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. Chest. 2011;139:591-599.

194. Tonnesen P, Mikkelsen K. Varenicline to stop long-term nicotine replacement use: a double-blind, randomized, placebo-controlled trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2013;15:419-427.

195. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. Jama. 2006;296:64-71.

196. Tsai ST, Cho HJ, Cheng HS, Kim CH, Hsueh KC, Billing CB, Jr., Williams KE. A randomized, placebo-controlled trial of varenicline, a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. Clinical therapeutics. 2007;29:1027-1039.

197. Williams KE, Reeves KR, Billing CB, Jr., Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. Curr Med Res Opin. 2007;23:793-801.

198. Wong J, Abrishami A, Yang Y, Zaki A, Friedman Z, Selby P, Chapman KR, Chung F. A perioperative smoking cessation intervention with varenicline: A

double-blind, randomized, placebo-controlled trial. Anesthesiology. 2012;117:755-764.