Evidence Synthesis

Number 134

Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation in Adults, Including Pregnant Women: A Review of Reviews for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA-290-2012-00015-1

Prepared by:
Kaiser Permanente Research Affiliates Evidence-based Practice Center
Kaiser Permanente Center for Health Research
Portland, OR

Investigators:
Carrie D. Patnode, PhD, MPH
Jillian T. Henderson, PhD, MPH
Jamie H. Thompson, MPH
Caitlyn A. Senger, MPH
Stephen P. Fortmann, MD
Evelyn P. Whitlock, MD, MPH

AHRQ Publication No. 14-05200-EF-1
September 2015

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2012-00015-1). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors acknowledge the following individuals for their contributions to this project: Tina Fan, MD, MPH, at AHRQ; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Catherine Chamberlain, MScPHP, MPH, BaSc, Michael Fiore, MD, MPH, MBA, Jennifer McClure, PhD, and Nancy Rigotti, MD, who provided expert review; the Centers for Disease Control and Prevention's National Center for Chronic Disease Prevention and Health Promotion and National Institute for Occupational Safety and Health and the National Cancer Institute, who provided federal partner review; and Keshia Bigler, Smyth Lai, MLS, and Kevin Lutz, MFA, at the Kaiser Permanente Center for Health Research.

Suggested Citation

Patnode CP, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation in Adults, Including

Pregnant Women: A Review of Reviews for the U.S. Preventive Services Task Force. Evidence Synthesis No. 134. AHRQ Publication No. 14-05200-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

Structured Abstract

Background: Tobacco use is the leading preventable cause of disease, disability, and death in the United States. Interventions to help adults quit smoking might stop or reduce tobacco-related illness.

Purpose: To systematically review evidence for the effectiveness and safety of pharmacotherapy and behavioral tobacco cessation interventions among adults, including pregnant women and those with mental health conditions, and to conduct a de novo search for primary evidence related to electronic nicotine delivery systems for adults.

Methods: We conducted a review of reviews and searched for existing systematic reviews published through August 1, 2014 in the following databases and organizations' websites: PubMed, PsycInfo, the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, the Centre for Reviews and Dissemination Health Technology Assessment, the Agency of Healthcare Research and Quality, British Medical Journal Clinical Evidence, the Canadian Agency for Drugs and Technologies in Health, Center for Disease Control and Prevention's Guide to Community Preventive Services, the Institute of Medicine, the National Institute for Health and Clinical Excellence, the National Health Service Health Technology Assessment Programme, and the Surgeon General. We included reviews that were published in the English language that systematically reported the effects of tobacco cessation interventions on health, cessation, or adverse outcomes. We excluded nonsystematic meta-analyses and narrative reviews and those that focused on harm reduction or relapse prevention. We conducted an *a priori* search for primary trial evidence related to the effectiveness and safety of electronic nicotine delivery systems (ENDS) (through March 1, 2015) and a search for pharmacotherapy among pregnant women (through August 15, 2014) to supplement the review of reviews methodology. Two investigators independently reviewed abstracts and full-text articles against a set of *a priori* inclusion and quality criteria. Discrepancies were resolved by consensus. One reviewer abstracted data into an evidence table and a second reviewer checked these data. We grouped reviews based on population (general adults, pregnant women, individuals with mental health conditions) and intervention (pharmacotherapy, behavioral, or combined interventions). We identified one or more reviews within each population and intervention subgroup that represented the most current and applicable evidence to serve as the basis for the main findings ("primary" reviews) and discussed complementary and discordant findings from other included reviews as necessary. We did not reanalyze any of the individual study evidence; we presented pooled analyses and existing point estimates from included reviews.

Results: We included 54 systematic reviews, 22 of which served as the basis for the primary findings. Among adults, nine reviews addressed the efficacy and/or harms of nicotine replacement therapy (NRT), bupropion hydrochloride sustained release (bupropion SR), and/or varenicline. None of these reviews reported on health outcomes. All three medications were found to be effective in increasing smoking quit rates compared with placebo or nondrug arms at 6 or more months followup. The pooled risk ratio (RR) for abstinence for NRT was 1.60 (95% confidence interval [CI], 1.53 to 1.68); for bupropion SR, RR 1.62 (95% CI, 1.49 to 1.76); and for varenicline, 2.27 (95% CI, 2.02 to 2.55). Combined NRT versus a single form of NRT showed a statistically significantly greater cessation effect in pooled analysis (RR 1.34 [95% CI,

1.18 to 1.51]). None of the drugs were associated with major cardiovascular adverse events, although NRT produced higher rates of all cardiovascular events (driven by minor events). One review on combined pharmacotherapy and behavioral interventions reported a relative increase in quitting by 82 percent versus nonpharmacotherapy usual care (RR 1.82 [95% CI, 1.66 to 2.00]). We included an additional 33 reviews that addressed behavioral tobacco cessation treatments among adults, including those that focused on specific subpopulations such as older adults. Compared with various controls, behavioral interventions such as in-person advice and support from clinicians, self-help materials, and telephone counseling had modest, but significantly increased, relative smoking cessation at 6 or more months (18% to 96%). For example, the pooled RR of physician advice versus no advice was 1.76 (95% CI, 1.58 to 1.96) for smoking cessation at 6 or more months followup. Only two trials addressed the efficacy and harms related to the use of electronic cigarettes and these trials suggested no benefit on smoking cessation among smokers intending to quit. We included eight reviews that focused on pregnant women that found significant benefits for perinatal health, including increased birth weight and reduced preterm birth. These benefits were evident with behavioral interventions, and suggested by data from some of the NRT trials, although that evidence was limited. Cessation during late pregnancy was greater among women receiving any type of behavioral intervention, with evidence most clear for counseling. Rates of validated cessation among women allocated to NRT (5% to 24%) compared with placebo (0% to 15%) were not statistically different, although few studies contributed data. Our reviews among individuals with depression or schizophrenia provided limited trial evidence on the efficacy of pharmacotherapy or behavioral interventions. There was, however, some evidence of a benefit for bupropion among those with schizophrenia and the addition of a mood management component to behavioral interventions for smokers with depression.

Conclusions: This review of reviews suggests that behavioral interventions and pharmacotherapy, alone or in combination, are effective in helping to reduce rates of smoking among the general adult population. Behavioral interventions, in particular, can assist pregnant women to stop smoking. Data on the effectiveness and safety of electronic nicotine delivery systems are limited. Future research should focus on direct comparisons between different combinations and classes of drugs; the incidence of serious adverse events related to medications for cessation; the efficacy and safety of ENDS; and pharmacotherapies for pregnant women and those with mental health conditions including evidence on health outcomes.

Table of Contents

Chapter 1. Introduction 1
Scope and Purpose 1
Condition Definition 1
Burden and Prevalence of Tobacco Use 2
Etiology and Natural History 3
Effect of Tobacco Cessation on Health Outcomes 3
Tobacco Cessation Interventions 5
Pharmacotherapy Tobacco Cessation Interventions 5
Behavioral Tobacco Cessation Interventions 5
Electronic Nicotine Delivery Systems 5
Current Clinical Practice in the United States 7
Recommendations of Others 8
Previous USPSTF Recommendations 9
Chapter 2. Methods 10
Scope of Review 10
Key Questions and Analytic Framework 10
Data Sources and Searches 10
Study Selection 11
Quality Assessment and Data Abstraction 12
Data Synthesis and Analysis 13
Expert Review and Public Comment 15
USPSTF Involvement 15
Chapter 3. Results 17
Literature Search 17
Adults: Results of Included Reviews 17
Key Question 1. Do Tobacco Cessation Interventions Improve Mortality, Morbidity, and Other Health Outcomes in Current Adult Tobacco Users? 18
Key Question 2. Do Tobacco Cessation Interventions Achieve Tobacco Abstinence in Current Adult Tobacco Users? 18
Key Question 3. What Adverse Events Are Associated With Tobacco Cessation Interventions? 36
Pregnant Women: Results of Included Reviews 40
Key Question 1. Do Tobacco Cessation Interventions Improve Mortality, Morbidity, and Other Health Outcomes in Pregnant Women? 40
Key Question 2. Do Tobacco Cessation Interventions Achieve Tobacco Abstinence in Pregnant Women? 43
Key Question 3. What Adverse Events Are Associated With Tobacco Cessation Interventions? 44
Individuals With Mental Health Conditions: Results of Included Reviews 46
Key Question 1. Do Tobacco Cessation Interventions Improve Mortality, Morbidity, and Other Health Outcomes in Smokers With Mental Health Conditions? 46
Key Question 2. Do Tobacco Cessation Interventions Achieve Tobacco Abstinence in Smokers With Mental Health Conditions? 47

Key Question 3. What Adverse Events Are Associated With Tobacco Cessation Interventions? 49
Chapter 4. Discussion 50
Summary of Evidence 50
General Adult Population 50
Pregnant Women 53
Individuals With Mental Health Conditions 54
Electronic Nicotine Delivery Systems 55
Limitations of the Review 56
Applicability 58
Comparison With 2008 Public Health Service Guideline and Other Related Reviews 59
Policy Implications of Tobacco Cessation Evidence 61
Future Research Needs 62
Conclusion 63
References 64

Figures

Figure 1. Past Month Cigarette Use Among Women Ages 15 to 44 Years, by Pregnancy Status: Combined Years 2002–2003 to 2011–2012
Figure 2. Analytic Framework: Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation Among Adults and Pregnant Women

Tables

Table 1. Characteristics of Included Existing Systematic Reviews by Population, Intervention, and Last Search Date
Table 2. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, Listed by Primary Review and Intervention Type
Table 3. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, as Listed in Text
Table 4. Summary of Tobacco Abstinence Results (KQ 2) From Reviews of Pharmacotherapy Tobacco Cessation Interventions Among Adults
Table 5. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention
Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention
Table 7. Summary of Tobacco Abstinence Results (KQ 2) From Reviews of Behavioral Counseling Tobacco Cessation Interventions Among Adults, by Type of Intervention
Table 8. Inclusion Criteria of Reviews on the Efficacy and Safety of Pharmacotherapy Tobacco Cessation Interventions Among Specific Adult Subpopulations, by Alphabetical Order
Table 9. Efficacy and Safety of the Use of Electronic Nicotine Delivery Systems for Smoking Cessation
Table 10. Adverse Event Results (KQ 3) of Pharmacotherapy Smoking Cessation Interventions Among Adults

Table 11. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Pregnant Women, by Alphabetical Order
Table 12. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy and Safety of Tobacco Cessation Interventions Among Pregnant Women
Table 13. Descriptive Characteristics of Included Trials of Pharmacotherapy Interventions Among Pregnant Women
Table 14. Summary of Perinatal Health Outcome Results (KQ 1) of Behavioral Tobacco Cessation Interventions Among Pregnant Women Within Chamberlain Review
Table 15. Summary of Tobacco Abstinence Results (KQ 2) From Reviews of Tobacco Cessation Interventions Among Pregnant Women
Table 16. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults With Mental Health Disorders, by Alphabetical Order
Table 17. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy and Safety of Tobacco Cessation Interventions Among Adults With Mental Health Disorders
Table 18. Summary of Evidence for the General Adult Population
Table 19. Summary of Evidence for Pregnant Women
Table 20. Summary of Evidence for Individuals With Mental Health Conditions

Appendixes

Appendix A. 2009 USPSTF Clinical Summary
Appendix B. Detailed Methods
Appendix C. Existing Systematic Reviews Included Studies
Appendix D. Excluded Systematic Reviews List
Appendix E. Poor-Quality Existing Systematic Reviews
Appendix F. Forest Plots
Appendix G. Ongoing Studies

Chapter 1. Introduction

Scope and Purpose

In 2009, the U.S. Preventive Services Task Force (USPSTF) reaffirmed their 2003 recommendation that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for those who use tobacco products (Grade A recommendation).[1] The original USPSTF recommendation (2003) and reaffirmation (2009) were based on the 2000 and 2008 updates of the Public Health Service (PHS) Clinical Practice Guideline "Treating Tobacco Use and Dependence".[2,3] Because there are no plans to update the PHS report, we undertook the current review to provide an updated synthesis of the evidence to assist the USPSTF in updating their 2009 recommendation. This review of reviews systematically evaluates the evidence for the benefits and harms of pharmacological and behavioral tobacco cessation interventions in adults, including pregnant women and those with mental illness. Given the increase in awareness, positive perceptions, and use of electronic nicotine delivery systems (ENDS), our review also synthesizes the primary trial evidence on the efficacy and safety related to this technology as a means for quitting conventional smoking.

Condition Definition

Tobacco is consumed in many forms including with cigarettes, pipes, cigars, cigarillos, little cigars, bidis (tobacco wrapped in tendu or temburni leaves), kreteks (clove cigarettes), smokeless tobacco (including chew, snuff including snus, and dissolvable tobacco in the form of strips, sticks, or lozenges), and smoking tobacco through a hookah or waterpipe. ENDS are devices that do not burn or use tobacco leaves. Instead, these devices deliver nicotine-containing aerosol that the user inhales by heating a solution that contains nicotine.[4] While there are ENDS that do not mimic cigarettes – such as electronic hookahs, electronic pipes, and electronic cigars – electronic cigarettes (e-cigarettes) are the most prevalent type of ENDS. We use the term ENDS when referring to the broader technology and the term e-cigarette when referencing and describing this technology specifically. A further description of ENDS, including the regulatory environment surrounding these products, is provided below.

Tobacco dependence is considered a chronic disease that requires specific treatment.[5,6] Tobacco-use disorder is defined as tobacco used to the detriment of a person's health or social functioning that includes the excessive use of tobacco products, including tobacco or nicotine dependence.[7] When an addicted user tries to quit, he or she typically experiences withdrawal symptoms that include irritability, attention difficulties, sleep disturbances, depression, increased appetite, and powerful cravings for tobacco. These symptoms may begin a few hours after the last cigarette and can quickly drive people back to tobacco use.[8] A number of behavioral factors (e.g., feel, smell, sight, social associations) can make withdrawal symptoms more acute.[9]

In this report, the term "tobacco use" indicates use of any tobacco product (not nicotine-delivery) and the term "smoking" refers to cigarette smoking alone.

Burden and Prevalence of Tobacco Use

Tobacco use is the leading preventable cause of disease, disability, and death in the United States. According to the 2014 Surgeon General's Report, cigarette smoking and exposure to tobacco smoke results in more than 480,000 premature deaths annually in the United States.[10] Tobacco use is associated with various forms of cancer, cardiovascular disease, respiratory disease, and reproductive disorders. Fifty years after the 1964 Surgeon General's report was published, research continues to identify diseases caused by cigarette smoking, including diabetes mellitus, rheumatoid arthritis, colorectal cancer, erectile dysfunction, tuberculosis, and congenital defects.[10] In addition to causing multiple diseases, cigarette smoking can cause inflammation and impair immune function.[10] Smoking during pregnancy is known to be causally related to higher risks of miscarriage, stillbirth, preterm birth, fetal growth restriction, placental abruption, certain congenital anomalies, and impaired lung function in childhood and beyond.[8,10-12] The role of nicotine as an important mediating agent in the relationship between tobacco smoking and poor pregnancy and perinatal health outcomes is increasingly evident, given observed associations even for smokeless tobacco use with stillbirth and preterm birth.[8,10,12]

In 2013, an estimated 17.8 percent (42.1 million) of U.S. adults were current cigarette smokers.[13] Over 76 percent (32.4 million) of these individuals smoked every day and 23.1 percent (9.7 million) smoked some days.[13] From 2005 to 2013, overall smoking prevalence declined from 20.9 to 17.8 percent.[13]

Significant disparities in cigarette smoking exist by age, sex, race/ethnicity, education, income level, and mental health status.[13] Adults aged 25 to 44 years have the highest rate of current cigarette smoking (20.1%), compared with adults aged 65 years or older (8.8%). Smoking prevalence is also significantly higher among men (20.5%) than women (15.3%). By race and ethnicity, smoking prevalence is highest among those reporting multiple races (26.8%), followed by American Indians/Alaska Natives (26.1%), non-Hispanic whites (19.4%), non-Hispanic blacks (18.3%), Hispanics (12.1%), and Asians (9.6%) Smoking prevalence also varies by education and income levels. By education, the rate of cigarette smoking is highest among adults with a graduate education development certificate (41.4%) and lowest among those with a graduate (5.6%) or undergraduate (9.1%) degree. Rates are also highest among people living below the poverty level (29.2%) compared with those living at or above this level (16.2%).[13] Rates of smoking are higher among adults with mental illness than among adults without mental illness.[14,15] In 2011, approximately 27.0 percent of individuals with a mental health disorder or substance use disorder were current smokers.[14] Among those with mental illness, the prevalence of smoking varies by specific diagnoses. In 2007, current smoking prevalence was highest for persons with schizophrenia (59.1%) and lowest for persons self-reporting phobias or fears (34.3%).[16] Approximately 46.4% of persons with bipolar disorder, 38.1% of persons with serious psychological distress, 37.2% of persons with attention deficit disorder or hyperactivity, and 35.4% of persons with dementia were current smokers.[16] The average number of cigarettes smoked in the past month was also higher among adults with any mental illness in the past year than among those who did not have any mental illness (331 versus 310 cigarettes).[17]

Among pregnant women aged 15 to 44 years, one in six smoked cigarettes during the previous month. The prevalence of current cigarette use was lower among pregnant women (15.9%) than

women who were not pregnant (24.6%) (**Figure 1**). This pattern was also observed among women aged 18 to 25 years (20.9% versus 28.2% for pregnant and non-pregnant women, respectively) and among women aged 26 to 44 years (12.5% versus 25.2%, respectively).[18]

Etiology and Natural History

Initiation of smoking typically begins in early adolescence at the average age of 15.4 years.[8] Data suggest that smoking prevalence in adolescents increases over time, peaks during young adulthood, and then declines as individuals age. This trajectory may vary, however, given differences in age at initiation of smoking, time to progress to daily smoking, and dependence symptoms. About one-third of individuals who have ever tried smoking become daily smokers.[8]

Tobacco dependence is a chronic condition and the majority of users make multiple quit attempts before achieving lasting success.[3] According to the National Health Interview Survey, 68.9 percent of current adult daily smokers reported they were interested in quitting smoking and 42.7 percent made a quit attempt during the past year.[10] An estimated 6.2 percent of current adult smokers had recently quit, 48.3 percent had been advised by a health care professional to quit smoking, and 31.7 percent had used medications and/or counseling when they made their quit attempt.[19] About 95 percent of people who try to stop smoking without a pharmacologic aid will continue to smoke or relapse within 1 year of the quit attempt.[8]

Research shows that the appearance of withdrawal symptoms early during the quit attempt is negatively associated with the ability to remain abstinent and avoid relapse.[8] On average, a second lapse occurs with 24 hours of the first lapse, and lapse to relapse occurs 3 to 5 weeks after the cessation attempt.[8] Factors influencing the path to relapse include past experiences with nicotine, confidence in the ability to quit smoking, severity of tobacco dependence, educational status, and situational indicators (e.g., partner smoking status, cigarette availability).[8]

Effect of Tobacco Cessation on Health Outcomes

The ultimate basis for recommending any preventive intervention is evidence that it would result in reduced morbidity and mortality. Such evidence is often missing or limited from intervention studies and intermediate outcomes must be used. This review focuses on smoking cessation as the main outcome as there is a substantial body of research indicating that smoking cessation results in important health benefits. These findings are summarized in this section.

Tobacco smoking increases mortality two- to three-fold.[20,21] Observational studies show that ex-smokers experience a gradual fall in this excess mortality (mortality can be increased in short-term quitters (< 5 years) because developing a smoking-related disease increases smoking cessation).[20] Quitting smoking before age 35 is associated with a mortality rate similar to that of never smokers.[21] While this benefit is decreased for older smokers who quit, it remains substantial. Jha and colleagues, for example, found that smokers who quit after age 50 still reduce their excess mortality risk by two-thirds.[21] Likewise, in a meta-analysis of 17 studies of smokers over age 60, Gellert and colleagues also found substantial mortality benefit at all ages,

including 80 and over, and increasing benefit with longer duration of abstinence.[22]

Causal inference from these observational data are supported by the Lung Health Study, which was a randomized controlled trial of an intensive smoking cessation intervention in patients with mild to moderate chronic obstructive pulmonary disease (COPD) compared with usual care (N=5,887).[23] The smoking cessation rate at 5 years in this study was 21.7 percent in the intervention group and 5.4 percent in usual care. After 14.5 years of followup the all-cause mortality rate was significantly lower in the intervention group (8.8 versus 10.4 per 1,000 person-years, p = 0.03). This difference would likely have been greater if more smokers in the intervention group had quit (49% never quit). The results of one other long-term followup study are also consistent with a causal effect of smoking cessation on mortality and morbidity. Rose and colleagues conducted a randomized controlled trial of physician smoking cessation advice in 1,445 high-risk men.[24] At 1 year, 51 percent of the intervention group reported not smoking compared with 10 percent in the control group. After 20 years, the rates of death, fatal coronary heart disease (CHD), and lung cancer all favored the intervention group, although none achieved statistical significance. For example, the all-cause mortality rate ratio in the intervention group compared with control was 0.93 (95% confidence interval [CI], 0.80 to1.09).[25] As with the Lung Health Study, these differences would likely have been larger if more men in the intervention group had quit; in addition, the smoking rate steadily declined in the control group over the first 10 years of followup, narrowing the intervention effect.

Tobacco smoking is a definitive risk factor for lung cancer with men who smoke having a 22-fold increased risk, and women who smoke having a 12-fold increased risk of acquiring the disease.[20] Smoking cessation, however, can greatly reduce this risk. Ten years after quitting, for example, the risk of developing lung cancer falls by half to two-thirds.[20] The most common smoking-related disease is CHD and here the benefit of quitting accumulates more rapidly, with a 50 percent decrease after 1 year and a return to nearly the same rate as never-smokers after 15 years.[20] Stroke risk also decreases after quitting, as evidenced by Kawachi and colleagues' findings in women that excess risks among former smokers largely disappeared from 2 to 4 years after quitting.[26] Likewise, Wannamethee and colleagues observed a halving of the risk of stroke after quitting tobacco use in men, although the risk remained marginally elevated, compared with never smokers.[27] Cessation is also associated with improvements in depression, anxiety, stress, psychological quality of life, and positive affect compared with continuing to smoke.[28] The effect is equal or larger among those with mental health disorders compared with those without.[28]

Smoking during pregnancy retards fetal growth by about 200 grams, doubles the risk of delivering a low birth weight baby, and increases fetal death by 25 to 50 percent.[20] Quitting smoking before or during the first 3 to 4 months of pregnancy eliminates this excess risk attributable to smoking.[20]

While almost all of the data linking smoking cessation to improved morbidity and mortality are observational, the breadth and consistency of the evidence over some 6 decades provides strong assurance that to the extent that counseling and treatment in primary care are effective in producing smoking cessation they will produce improved morbidity and mortality at a magnitude exceeding that of almost any other medical therapy.

Tobacco Cessation Interventions

Various pharmacological and behavioral methods designed to assist adults and pregnant women stop smoking are available. Behavioral interventions and pharmacotherapy are believed to have complementary modes of action and independently improve the chances of maintaining long-term abstinence.[3]

Pharmacotherapy Tobacco Cessation Interventions

Seven U.S. Food and Drug Administration (FDA)-approved over-the-counter (OTC) and prescription medications for treating tobacco dependence are now available.[29] These include three OTC nicotine replacement products (transdermal nicotine patches, nicotine lozenges, and nicotine gum), two prescription-only nicotine replacement products (nicotine inhaler or nasal spray [Nicotrol®]); and prescription-only bupropion hydrochloride sustained release (Zyban® or generic) (bupropion SR, hereafter) and varenicline tartrate (Chantix®) – that do not contain nicotine. Although Wellbutrin SR® is not indicated for smoking cessation treatment, it contains the same active ingredient as Zyban®. These individual medications can also be used in combination in an attempt to improve quit rates. Recent changes by the FDA allow labeling statements for OTC NRT products to be modified whereby deleting the warning that states that users should "not use the NRT product if they continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing product".[30] Manufacturers of OTC NRT products have been encouraged to submit labeling supplements to the FDA to reflect this change.[30] Other medications are used clinically to treat tobacco dependence, including clonidine (antihypertensive) and nortriptyline (antidepressant), but these are not FDA approved for smoking cessation.[29,31]

Behavioral Tobacco Cessation Interventions

Specific behavioral interventions include, but are not limited to: self-help materials (e.g., written materials, videos, audiotapes, computer), phone-based interventions, quitlines, brief provider-delivered interventions (e.g., advice from a physician or nurse), intensive counseling delivered on an individual basis or in a group including motivational interviewing, mobile phone and text messaging interventions, biomedical risk assessment, and combinations of these approaches. These interventions teach individuals to recognize high-risk situations and develop coping strategies to deal with them. Complementary and alternative therapies, such as acupuncture, acupressure, laser therapy, electrostimulation, hypnotherapy, and the consumption of herbals (e.g., St. John's Wort) have also been used as tobacco cessation aids alone or as adjuncts to other treatments.

Electronic Nicotine Delivery Systems

ENDS, including e-cigarettes, are battery-powered devices that contain a cartridge filled with nicotine and other additives. Over 400 e-cigarette brands exist with a wide range of designs.[32] Most ENDS aim to simulate the visual, sensory, and behavioral aspects of smoking tobacco

cigarettes.[33] Common e-cigarette components include an electronic heating element, a battery, and a cartridge that houses a liquid solution (i.e., e-liquid, juice) of propylene glycol and/or glycerol (glycerin), with various levels of nicotine (including no nicotine).[34] Other components of the solution include water, ethanol, and various additives that vary in presence and amount between brands.[34] E-cigarettes are available in disposable or rechargeable versions. While disposable versions must be discarded after the liquid is gone, rechargeable versions, including those with "tank systems," may be used indefinitely because the battery can be recharged with a computer USB port or wall outlet. In this case, the user replaces the cartridge as often as they would like. Cartridges are available in a broad range of flavors (e.g., tobacco, strawberry, chocolate) and are usually labeled with their nicotine content. Depending on the brand, each cartridge is designed to produce about 250-400 puffs, which is equivalent to 1-2 packs of tobacco cigarettes. Because e-cigarettes are developed by a variety of manufacturers, the contents vary widely and in some cases are not consistent with product labeling.[34-37]

Currently, only ENDS that are promoted for therapeutic purposes (i.e., for cessation use) are regulated by the FDA.[38] Companies who wish to make such claims must apply to the FDA's Center for Drug Evaluation and Research. To date, we are aware of no manufacturers that have submitted approval packages for this purpose. On April 24, 2014, the FDA announced that it would enact rules to extend its authority to cover ENDS, deeming them to be subject to regulation as tobacco products.[39] Under the proposed rules, which were open for public comment through August 8, 2014, manufacturers would be required to disclose their products' ingredients, report harmful and potentially harmful components, and all regulated products would have to carry health warnings. Any claims that the products had lower health risks or other health benefits could be made only after FDA review and approval. In addition, sale of electronic cigarettes to anyone under age 18 years would be prohibited. The proposed rules would not ban advertising or internet sales of the products, nor the use of flavoring, all of which are believed to attract young nonsmokers. As of present, the proposed rules have not been enacted; we presume that public comments are under review by the FDA.[40]

Awareness and current use of ENDS have increased over recent years among current and former smokers as well as never smokers. In the United States, awareness of e-cigarettes among adults increased from 40.9 percent in 2010 to 79.7 percent in 2013, concurrent with a rise in current use (1.3% to 1.9% from 2010 and 2011 to 2012 and 2013, $p < 0.05$).[41,42] The use of e-cigarettes was particularly prevalent among current cigarette smokers, with over one-third (36.5%) reporting they had ever used e-cigarettes and 9.4 percent concurrently using e-cigarettes and conventional cigarettes in 2013. This compares with only 9.6 percent and 1.3 percent of former smokers who reported ever and current use of e-cigarettes, respectively.[41] Results of the International Tobacco Control Four-Country Survey found that current use of e-cigarettes did not differ among adults in the United States, Canada, the United Kingdom, or Australia. While e-cigarette use did not vary, awareness was significantly different across countries, with adults in the United States reporting the highest awareness (73.4%).[43] One study found that smokers with mental health conditions are more likely to have tried e-cigarettes (14.8%) and to be current users of e-cigarettes (3.1%) than those without mental health conditions (6.6% and 1.0%, respectively).[44]

The rapid increase in the advertising, sales, and use of ENDS has evoked a vigorous debate in the tobacco control community about the public health impact of ENDS, how to best regulate

them, and their role in tobacco cessation.[45-60] Proponents of ENDS argue that because e-cigarettes offer both nicotine replacement and behavioral and sensory aspects similar to conventional cigarettes without the inhalation of tobacco smoke, they represent an ideal candidate as a cessation or harm reduction tool.[61-63] Significant questions remain, however, regarding ENDS' impact on individual and population health, including concerns related to the initiation of nicotine addiction in adolescents, the potential for progression to conventional tobacco use among non-tobacco users, long-term dual use among current smokers, relapse among former smokers, and the inclusion of harmful or potentially harmful ingredients.[10,59,64-66] In addition, nicotine exposure can have adverse effects on reproductive health and adolescent brain development.[10]

Current Clinical Practice in the United States

Primary care clinicians are in the unique position of having recurring opportunities to address smoking cessation efforts with their patients who smoke. Studies have shown that approximately 70 percent of smokers see a physician annually, which provides an ideal chance to discuss health behaviors and potential interventions.[67,68] Despite USPSTF recommendations that clinicians identify, counsel, and treat smokers, reported data suggest that physicians do not consistently adhere to this recommendation.

In 2012, the Centers for Disease Control and Prevention (CDC) reported the findings of an audit of the National Ambulatory Medical Care Survey and the National Health Interview Survey through 2005-2009. This audit sought to evaluate the progress made towards meeting the Healthy People 2020 objectives related to tobacco use screening and counseling among adults.[68] The CDC reported that during this 3-year period, current tobacco users made 340 million visits (17.6% of total visits) to office-based physicians. During these visits, only 20.9 percent reported receiving tobacco counseling from their provider and 7.6 percent reported receiving a prescription medication for treating tobacco dependence. Close to half-a-billion visits (62.7% of all visits) were found to include tobacco screening.

The rates of counseling and treatment were found to vary depending on patients' age, race, insurance status, physician status, and physician specialty. Overall, patients classified as non-Hispanic whites were more likely to receive counseling than Hispanic patients (64.1 versus 57.8%). Among current tobacco users, younger patients (aged 25 to 44 years) reported receiving less counseling (17.9%) than patients aged 45 to 64 years (22.7%).[68] This is unfortunate because younger patients have more failed quit attempts than older patients and, additionally, quitting prior to the age of 50 substantially decreases smoking-related health outcomes.[68,69] Patients with workers' compensation, and those whose insurance status was unknown were less likely to receive counseling than those with private insurance, self-payers, Medicaid, and Medicare patients. Patients were more likely to receive counseling from their primary care physician (26.9%) than from other health care providers (15.5%) and internal medicine and cardiovascular disease physicians were more likely to provide tobacco cessation counseling (32.5% and 35.4%) than family or obstetrics/gynecology physicians (23.5 and 19.7%). Psychiatrists ordered tobacco cessation prescriptions more than any other specialty (17.7%).[68]

Other published studies have reported similar rates of tobacco cessation interventions by physicians. A 2005 audit of electronic medical records of 522 Boston-area smokers, for example, found that 62 percent were asked about their smoking status by their physician, 27 percent were advised to quit, and only 20 percent received any assistance in quitting (including counseling or referral to support programs).[70] A 2007 random sample telephone survey of Medicaid-enrolled smokers and recent quitters (n=563) found that 87 percent were asked about their smoking status, 65 percent were advised to quit, and only 24 percent received assistance with quitting.[71] These findings are analogous to the rates provided in a recent systematic review of tobacco cessation interventions, which reported that 40 to 70 percent of smokers recounted receiving cessation advice and less than 20 percent received assistance with quitting.[72] Barriers to providing tobacco-related interventions reported by physicians include a lack of counseling skills, knowledge, motivation, and time, as well as insufficient reimbursement, patient motivation, and system support.[73-75]

There are limited data available on the screening or counseling practices related to ENDS among primary care clinicians. The first study to measure physicians' attitudes towards the use of e-cigarettes as cessation devices was conducted in 2013 among a sample of 787 North Carolina physicians (response rate=31%). The study found that two thirds of the physicians indicated that e-cigarettes are a helpful aid for smoking cessation and 35 percent recommended them to their patients.[76] Almost 65 percent of the physicians believed that e-cigarettes lower the risk of cancer for patients who use them instead of smoking cigarettes, and 13 percent incorrectly believed that e-cigarettes have been approved by the FDA for smoking cessation.[76] A 2012 survey of members of the American College of Obstetricians and Gynecologists (ACOG) found that 53 percent of respondents reported screening pregnant women for chewing tobacco, snuff/snus, e-cigarettes, and dissolvables all or some of the time. While approximately 14 percent of those surveyed reported that e-cigarettes have no adverse health effects, only 5 percent felt fully informed on the safety of these products.[77]

Recommendations of Others

The 2009 USPSTF recommendation and 2008 PHS Guideline are endorsed by, or are generally consistent with the recommendations of other national and international organizations, including those from the American Medical Association, the American Dental Association, the American Nurses Association, ACOG, and the Institute of Medicine. In addition, the Community Preventive Services Task Force recommends worksite-based incentives and competitions when these efforts are combined with other individual support interventions, increasing the unit price of tobacco products, mass-reach health communication interventions, quitline interventions, and smoke-free policies to encourage tobacco cessation among adults.[78]

The World Health Organization recently released recommendations for the prevention of tobacco use during pregnancy in 2013.[12] The recommendations were based on a review of reviews, and ratings of the quality of the evidence. A strong recommendation for advice and psychosocial interventions for pregnant women who are smokers was given. The panel recommended against the use of bupropion or varenicline for smoking cessation based on very low quality evidence, but could not make a recommendation for or against NRT use during pregnancy. Accordingly, a

strong recommendation for further research on pharmacotherapy for smoking cessation during pregnancy was made.

Previous USPSTF Recommendations

In 2003, the USPSTF reviewed the evidence for tobacco cessation interventions in adults and pregnant women contained in the 2000 U.S. Public Health Service (PHS) clinical practice guideline "Treating Tobacco Use and Dependence"[2] and found that the benefits of these interventions substantially outweighed the harms. In 2008, the USPSTF reviewed new evidence in the updated PHS guideline[3] and determined that the net benefits of screening and tobacco cessation interventions in adults and pregnant women remain well established. The USPSTF found no new substantial evidence that could change its conclusions and, therefore, reaffirmed its previous recommendations.

Thus, in 2003 and 2009, the USPSTF recommended: 1) that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for those who use tobacco products (A recommendation) and 2) that clinicians ask all pregnant women about tobacco and provide augmented, pregnancy-tailored counseling for those who smoke (A recommendation).[1] The clinical summary of the 2009 USPSTF recommendations can be found in **Appendix A**.

Chapter 2. Methods

Scope of Review

We relied primarily on a review of reviews method for this update. This was the most appropriate approach considering the large number of behavioral and pharmacologic tobacco cessation interventions and the availability of multiple existing systematic reviews on this subject for both adults and pregnant women. In general, a review of reviews focuses on a broad condition or problem for which there are two or more potential interventions. This approach highlights existing systematic reviews that address these potential interventions and their results.[79-81] To conduct this review of reviews we: 1) searched for reviews; 2) selected reviews; 3) assessed the quality of reviews; 4) determined the use of reviews; 5) abstracted review details and findings; and 6) synthesized findings across reviews.[81] A typical Analytic Framework, Key Questions (KQs), and inclusion/exclusion criteria are outlined as they relate to the objectives of the review of reviews. We did not search for, or screen, original research (with the exceptions noted below), replicate quality rating or data abstraction of original studies, or replicate review-specific analyses (including meta-analyses). We decided *a priori* to conduct a de novo search for primary evidence related to the effectiveness and safety of ENDS. In addition, before initiating our review, we established that we would consider a search for primary research for specific interventions and/or questions if no recent fair- or good-quality reviews were identified for the topic.

Key Questions and Analytic Framework

With input from the USPSTF, we developed an Analytic Framework (**Figure 2**) and three KQs using the USPSTF's methods to guide the literature search, data abstraction, and data synthesis for this topic.[82] The proposed Analytic Framework and KQs were posted on the USPSTF's website for public comment for 4 weeks. We revised the Analytic Framework and KQs based on public comment. The USPSTF provided final approved. We examined the following KQs:

1. Do tobacco cessation interventions improve mortality, morbidity, and other health outcomes in current adult tobacco users, including pregnant women and individuals with mental health conditions?
2. Do tobacco cessation interventions achieve tobacco abstinence in current adult tobacco users, including pregnant women and individuals with mental health conditions?
3. What adverse events are associated with tobacco cessation interventions?

Data Sources and Searches

We searched the following databases for relevant reviews through August 1, 2014: PubMed, PsycInfo, the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews (CDSR), and the Centre for Reviews and Dissemination Health Technology Assessment (**Appendix B**). In addition to these database searches, we searched the websites of

the following organizations: the Agency of Healthcare Research and Quality (AHRQ), British Medical Journal Clinical Evidence (through August 7, 2013), the Canadian Agency for Drugs and Technologies in Health, CDC's Guide to Community Preventive Services, the Institute of Medicine, the National Institute for Health and Clinical Excellence, the NHS Health Technology Assessment Programme, and the Surgeon General. We restricted our searches to articles in the English-language published since January 2009. We also examined the reference lists of all of our included reviews to identify other studies for inclusion. We supplemented our searches with suggestions from experts and reviews identified through news and table-of-contents alerts from sources such as ScienceDirect (Elsevier, Maryland Heights, MO) and *Tobacco Control*. We also searched for potentially relevant in-process or planned reviews as indicated by review protocols through AHRQ, CDSR, the Centre for Reviews and Dissemination PROSPERO register, and the journal *Systematic Reviews.*

In addition to the search for reviews, we conducted two separate searches for primary evidence. The first search focused on studies addressing ENDS. We conducted searches in the following databases: CDSR, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Scopus from January, 2008 through May 13, 2014 (**Appendix B**). Given the rapidly emerging research on ENDS, we also subscribed to and received weekly email alerts from PubMed on newly published articles related to ENDS through March 1, 2015. Finally, we reviewed the reference lists of nine related systematic or narrative reviews to identify studies for potential inclusion.[83-91]

The second search was for primary evidence related to pharmacotherapy tobacco cessation interventions among pregnant women. While we identified five relevant reviews on this subject (described in our Results section), the small number of included studies in each existing review and the imprecision of the effect estimate warranted an updated search and synthesis of more recent evidence. As such, we conducted searches for primary evidence on pharmacotherapy among pregnant women in Medline, CENTRAL, PubMed, PsycInfo from January, 2012 through August 15, 2014 (**Appendix B**). Finally, we searched *ClinicalTrials.gov* for ongoing pharmacotherapy tobacco cessation trials among pregnant women that were listed as "recruiting," "active, not recruiting," "not yet recruiting," "completed," or "terminated" to identify any studies underway that might be of relevance for ongoing evaluation.

We imported the literature from these searches directly into version 12 of Reference Manager® (Thomson Reuters, New York, NY), a bibliographic management database.

Study Selection

We developed criteria for inclusion and exclusion of existing systematic reviews based on our understanding of the literature and the existing PHS Guideline (**Appendix B Table 1**). Generally, we included studies if they were systematic reviews, with or without meta-analysis, that: (1) examined the effectiveness of tobacco cessation interventions for adults or pregnant women and were linked to primary care or took place in a general adult population; and (2) were published in English, from January 2009 to present. We excluded nonsystematic narrative and discussion reviews. We also excluded reviews that focused on tobacco harm-reduction or relapse

prevention interventions or nonfirst-line FDA approved cessation medications. We excluded reviews that only or primarily evaluated interventions among children and adolescents and broader public health strategies. We only included the most recent version of updated reviews. We kept detailed records of all included and excluded reviews, including the reason for their exclusion.

We outlined separate inclusion and exclusion criteria when considering primary evidence related to pharmacotherapy interventions among pregnant women and for ENDS. For pharmacotherapy interventions among pregnant women, we used the criteria outlined by Coleman and colleagues.[92] Accordingly, we included randomized controlled trials (RCTs) with designs that permitted assessment of the independent effects of any type of NRT or any other first-line pharmacotherapy on smoking cessation. Included trials also had to provide very similar (or identical) levels of behavioral support to participants in the treatment and control groups. We excluded quasi-randomized, cross-over, within-participant, and observational designs. We required that studies take place in developed countries as defined as "very high" on the 2013 human development index of the United Nations (http://hdr.undp.org/en/statistics), which is consistent with the broader review literature.

For primary evidence related to the efficacy (KQ1-KQ2) and safety (KQ3) of ENDS, we included RCTs in which smokers were randomized to ENDS or a control condition, such as a placebo device or a no-intervention condition. We excluded all observational designs. We only included studies if they reported a health outcome (KQ1) or a measure of smoking abstinence (KQ2) at least 6 months after baseline assessment or adverse events (KQ3) at any point after treatment started. We excluded studies that only reported intermediate smoking outcomes (e.g., desire to smoke, withdrawal symptoms, or quantity of conventional cigarettes smoked). Again, we required that studies take place in developed countries consistent with the broader review literature.

Two reviewers independently screened all records identified in the searches on the basis of their titles and abstracts, using the inclusion/exclusion criteria as a guide. Subsequently, two reviewers assessed the full text of potentially relevant systematic reviews and primary studies using a standard form outlining the eligibility criteria. We resolved disagreements through discussion.

Quality Assessment and Data Abstraction

We used a slightly modified version of the AMSTAR (Assessment of Multiple Systematic Reviews) tool to quality rate included systematic reviews for this review of reviews.[93,94] The original AMSTAR tool contains 11 evaluation criteria, such as whether study selection and data abstraction are conducted by at least two reviewers, whether publication bias was assessed, and whether conflicts of interest were reported. To adapt the AMSTAR tool to fit USPSTF procedures, we deleted one item that assessed whether the status of the publication was used as an inclusion criterion because of low inter-rater agreement and difficulty with scoring.[94] We also split two of the items into separate questions to more accurately account for the extent of duplicate study selection *and* duplicate data extraction, and the sources of potential conflicts of interest (i.e., both the systematic review and included studies) (**Appendix B Table 2**).

For primary evidence, we used standard criteria developed by the USPSTF to assess the quality of included evidence.[82] We examined potential risks of bias, including randomization and measurement procedures (including blinding and consistency between groups); comparability of the groups at baseline; overall and group-specific attrition; intervention fidelity and participant adherence; and the appropriateness of the statistical procedures, including methods for handling missing data.

We applied the typical USPSTF quality scores (i.e., good-quality, fair-quality, or poor-quality) for both reviews and primary evidence after reviewing the number and seriousness of the threats to validity. Reviews assigned a good-quality rating affirmatively addressed all or most AMSTAR evaluation criteria whereas those rated as fair-quality did not meet a number of standards that may have affected the review's comprehensiveness, reproducibility, and conclusions (e.g., no dual study selection, did not account for individual study-level quality assessment in formulating conclusions, did not disclose potential conflicts of interest of included studies or review authors). Those rated as poor-quality contained a serious flaw or flaws that likely biased or invalidated the results. We excluded all poor-quality systematic reviews and primary trials. At least two independent reviewers assessed the quality of the included systematic reviews and primary evidence. We resolved discrepancies through discussion.

We abstracted descriptive data about each review into detailed abstraction tables. One reviewer completed primary data abstraction and a secondary reviewer checked all data for accuracy and completeness. Data collection included general characteristics of the review (e.g., author, year assessed up-to-date); clinical characteristics of included studies (e.g., age and clinical characteristics of population, type of intervention, outcomes reported); methodological features (e.g., design of primary studies included in review, search strategy, language and publication restrictions, methods for quality assessment of primary studies); and results (e.g., number of primary studies included, review findings). We abstracted and described data from primary studies directly in the report narrative.

Data Synthesis and Analysis

Given the number of fair- and good-quality reviews that met our eligibility criteria, we developed a method to identify one or more reviews within each population and intervention subgroup that represented the most current and applicable evidence to serve as the basis for the main findings (called "primary" reviews, hereafter). First, we categorized all included reviews according to the overall discrete population of interest (i.e., adults, pregnant women, or patients with mental health conditions) and type of tobacco cessation intervention (i.e., pharmacotherapy, behavioral, and/or combination). Within each group, we listed the reviews in chronological order by the last search date with the most recent search listed first (some reviews were listed more than once in the table if they addressed multiple populations or intervention types). Next, we compared the included studies within each review to evaluate the comprehensiveness of each review and noted concordance and discordance in the included primary literature (**Appendix C**). When we encountered highly discordant bodies of evidence, we sought explanation for the difference by examining the inclusion and exclusion criteria for each review. For example, if the most recent review for a given category did not appear to be the most comprehensive review in

terms of the number of included studies, we examined to what extent the inclusion criteria (e.g., allowable study designs, outcomes of interest) may have influenced the discrepancy in included studies. We also looked at individual included studies as necessary to ensure that the potential primary reviews did not omit important studies. Finally, we reviewed the inclusion and exclusion criteria and data analysis procedures of each review to determine the most applicable evidence. Box 1 describes the full set of criteria we applied to identify the primary review for each population and intervention. We reviewed the remaining reviews ("secondary" reviews) for complementary or discordant findings. These reviews are referenced throughout our report. In general, the results across reviews within each population and intervention grouping were consistent with one another and thus, we do not elaborate on these consistencies within the results.

Box 1. Criteria for Choosing the Primary Existing Systematic Reviews

1. The search is more up-to-date than other reviews for the same population/intervention group.
2. The included studies apply inclusion/exclusion criteria that offer the most relevant and credible evidence (i.e., based on included study designs, populations, setting, followup > 6 months, and outcomes).
3. There are relatively more (or equal) included studies of the ideal study design compared with other reviews for the same population/intervention.
4. Appropriately conducted pooled results are presented, with or without meta-regression or subgroup analysis.
5. The quality of the review is more favorable than other reviews for the same population/intervention.

We descriptively summarized the characteristics of the primary evidence reviews into evidence tables. We did not reanalyze any of the individual study evidence. We used the pooled analyses and existing point estimates presented in the included reviews as appropriate. For reviews that included meta-analyses, we conducted comparisons of the pooled estimates of efficacy for each intervention versus comparator and took the definition of abstinence (continuous, point prevalence) and the length of followup into consideration. When extracting pooled estimates from the reviews, we considered the statistical validity of the meta-analytic results available. Following current developments in methods for pooling data in general, we do not report pooled estimates for fewer than five studies because necessary adjustments for observed or unobserved heterogeneity is inestimable or likely to be biased.[95,96] Pooling 10 or fewer studies warrants some caution in interpretation, as there are documented biases in the DerSimonian-Laird (DL) estimates most commonly used to account for random error. In this range, we interpreted pooled estimates while considering the proximity of the confidence interval to the null value (when available) and recognizing that a DL estimated confidence interval could underestimate variance. For all pooled estimates, we reported the I^2 to evaluate statistical heterogeneity based on Cochrane Collaboration thresholds, with ranges from 30 percent to 60 percent possibly representing moderate heterogeneity, from 50 percent to 90 percent possibly representing substantial heterogeneity, and above 75 percent representing considerable heterogeneity.[97] In cases of considerable statistical or qualitative heterogeneity of effect estimates, we presented forest plots to summarize and describe the data or narratively described the results, but caution readers in drawing conclusions from pooled estimates based on few trials. We also presented subgroup results related to the intensity or type of intervention, when available, and when the

review identified other factors that influenced the effectiveness of interventions. Overall, we evaluated the appropriateness of meta-analytic procedures and used our technical judgment to interpret pooled analyses accounting for limitations or concerns from heterogeneity, statistical approaches, or other factors. We obtained permission to republish review forest plots or in the absence of review-generated forest plots, created our own based on the data presented in the review. We provided narrative results for reviews that did not include meta-analyses.

The primary outcome for KQ2 was smoking cessation at 6 months or longer followup using the strictest definition of abstinence available in each review. We abstracted results at both 6- and 12-months followup if the reviews presented both. In most cases, the reviews reported the "longest followup" result and required at least 6 months followup. The preferred outcome in most reviews was continuous abstinence (i.e., completely abstinent from quit date to followup allowing for up to five cigarettes) or prolonged abstinence (i.e., typically allows a 'grace period' following the quit date to allow for lapses) over point prevalence abstinence (i.e., abstinent at a particular point in time such as 7 days or 30 days before followup and thus includes a mix of recent and continuous quitters).[98] Biochemical verification of self-reported abstinence was not required in most reviews, but validated outcomes were used where reported. Within the reviews, the 7-day point prevalence abstinence was typically preferred when more than one point prevalence abstinence rate was reported; 30-day abstinence was classified as point prevalence abstinence rather than continuous abstinence. All included reviews used analyses based on intention-to-treat principles in which participants lost to followup who could not be classified definitively as nonsmokers were counted as smokers, when reported.[98]

Expert Review and Public Comment

A draft of the Analytic Framework, KQs, and inclusion/exclusion criteria was posted on the USPSTF's website for public comment from November 7 to December 4, 2013. We received comments from eight public commenters and partner organizations. These comments led to no changes to the research plan that changed the scope of the review or our approach to synthesizing the evidence. Minor clarifying text, however, was added based on public comments. A final research plan was posted on the USPSTF's website on February 6, 2014. The full draft report was reviewed by experts and Federal partners from September 26 through October 17, 2014. We compiled and addressed (where appropriate) the comments received from invited reviewers. Additionally, a draft of the full report was posted on the USPSTF's Web site from May 5 through June 1, 2015. A few comments were received during this public comment period; there were no changes made to the report based on these comments.

USPSTF Involvement

We worked with three USPSTF liaisons at key points throughout this review, particularly when determining the scope and methods for this review and developing the Analytic Framework and KQs. The USPSTF liaisons approved the final Analytic Framework, KQs, and inclusion and exclusion criteria after revisions reflecting the public comment period. AHRQ funded this review

under a contract to support the work of the USPSTF. An AHRQ Medical Officer provided project oversight, reviewed the draft report, and assisted in the external review of the report.

Chapter 3. Results

Literature Search

We identified 54 existing systematic reviews that met our eligibility criteria.[92,99-146,147-154] Of the 114 full-text articles that were reviewed, the most common reasons for exclusion were study design (i.e., was not a systematic review; k=25), intervention type (e.g., harm reduction interventions, second-line or off-label medications; k=7), and poor-quality rating (k=8) (**Appendix B Figure 1**; **Appendix D**). **Appendix E** lists the eight reviews we excluded for receiving a poor-quality rating and the rationale for this rating.

As described in the methods section, we selected 22 of the 54 included reviews to serve as the basis for the primary findings of this review. We chose these reviews based on their comprehensiveness, appropriateness, and quality ratings. We listed the remaining 32 reviews in the descriptive tables; the results of these reviews were generally consistent in terms of the significance and magnitude of effects in relation to the primary reviews. **Table 1** lists all 54 of the included reviews categorized by population and intervention approaches, with other descriptors including quality rating, the month and year through which the search was up-to-date, and the KQs the reviews addressed. This review of reviews addresses discrete populations of interest separately for each KQ: general adult population, pregnant women and adults with mental health conditions. Within each population, results are organized first by KQ and then by subpopulation-intervention specific categories. Within adults, we have general adult populations or specific adult subpopulations in combination with different types of interventions (i.e., pharmacotherapy or behavioral [or some combination of these], and e-cigarettes). **Table 1** displays the number of primary reviews for each population-intervention category; primary reviews for each group are indicated with an asterisk.

Adults: Results of Included Reviews

Of the 54 included reviews, 43 addressed tobacco cessation interventions among a general adult population. Nine of these reviews evaluated the effectiveness and/or adverse events related to pharmacotherapy[120,121,128-130,135,140,145,154] and one addressed combined pharmacotherapy and behavioral interventions.[138] An additional 26 reviews addressed behavioral tobacco cessation treatments among adults.[100,102-104,106,108,111-114,118,119,122,124,131,132,136,137,139,141,142,144,147,148,151,152]
Seven of these 43 reviews focused on specific subpopulations within the general adult population (i.e., ethnic minorities, young adults, older adults, and smokeless tobacco users) and included behavioral and/or pharmacotherapy interventions.[109,115,123,126,134,150,153]

Key Question 1. Do Tobacco Cessation Interventions Improve Mortality, Morbidity, and Other Health Outcomes in Current Adult Tobacco Users?

Pharmacotherapy Interventions Among Adults

We identified no existing systematic reviews that assessed pharmacotherapy interventions among adults that reported the effects of interventions on mortality, morbidity, or other health outcomes.

Behavioral Interventions Among Adults

A single systematic review reported the effect of one behavioral tobacco cessation intervention on health outcomes. This review, conducted by Stead and colleagues (2013a),[139] searched for evidence through January, 2013 and included studies assessing the effectiveness of advice from medical practitioners on mortality and morbidity as a secondary outcome. This review's primary outcome was smoking cessation. The review included RCTs that were conducted among adult nonpregnant smokers that compared physician advice interventions with no advice, usual care, or with differing levels of physician advice. The review included one study that reported the effects of a stop smoking intensive intervention that included advice, written materials, and one followup visit on health outcomes among males considered to be at high risk of cardiorespiratory disease (n=1,445).[24] Within this study, there were no statistically significant differences in the rates of total mortality, coronary disease mortality, and lung cancer incidence and mortality at 20 years followup. At 33 years followup, there was a significantly smaller number of deaths from respiratory illnesses among intervention versus control participants.[25] None of the other reviews reported the effects of tobacco cessation interventions on health outcomes.

Key Question 2. Do Tobacco Cessation Interventions Achieve Tobacco Abstinence in Current Adult Tobacco Users?

Pharmacotherapy Interventions Among Adults

We included six reviews that evaluated the effectiveness of pharmacotherapy interventions on tobacco cessation among current tobacco users (**Tables 1** and **2**).[120,121,129,140,145,154]

Nicotine Replacement Therapy

Three reviews evaluated the evidence for the effectiveness of NRT on smoking cessation.[129,140,145] The most recent good-quality review, conducted by Stead (2012a),[140] systematically searched for evidence through July, 2012. This review included RCTs or quasi-RCTs that compared NRT (including chewing gum, transdermal patches, nasal and oral spray, inhalers and tablets or lozenges) with placebo or no NRT control among adult smokers who were motivated to quit. Two other fair-quality reviews, conducted by Mills[129] and Tran,[145] also evaluated evidence related to the effectiveness of NRT for smoking cessation, searching through January, 2012 and February, 2009, respectively (**Table 2**). We used the Stead (2012a) review as the basis for the primary evidence of NRT effectiveness because of its comprehensiveness and

quality. The Stead review included most of the included evidence in the Mills[129] and Tran[145] reviews (**Appendix C Figure 1**).[140]

Stead (2012a) included 150 RCTs that ranged in size from fewer than 50 to over 3,500 participants (median: 240) (**Table 3**). The included trials generally recruited individuals who smoked at least 15 cigarettes a day and the average number of cigarettes smoked was over 20 per day in most studies. The majority of the studies took place in North America (k=77) or Europe (k=60). The primary analysis (i.e., the efficacy of one or more types of NRT compared with a placebo or a control group receiving no NRT) consisted of 117 trials reporting122 comparisons among 51,265 participants (**Table 4**). Of these 117 studies, 55 trials evaluated nicotine gum, 43 trials evaluated transdermal nicotine patch, six evaluated an oral nicotine tablet or lozenge, five evaluated offering a choice of products, four evaluated intranasal nicotine spray, four evaluated nicotine inhaler, one evaluated oral spray, one evaluated providing patch and inhaler, and one evaluated providing patch and lozenge. Seventy-five percent of the 55 trials that compared nicotine gum to a control provided the 2 milligram (mg) dose, while the remaining trials provided 4 mg. The treatment periods were usually 2 to 3 months, but ranged from 3 weeks to 12 months. Many of the trials included a variable period of dose tapering, but most encouraged participants to be gum-free by 6 to 12 months. Among the nicotine patch trials (k=43), the typical maximum daily dose was 15 mg for a 16-hour patch, or 21 mg for a 24-hour patch. Eight trials directly compared a higher dose patch to a standard dose patch. The minimum duration of therapy ranged from 3 weeks to 3 months. In the nicotine tablet or lozenge studies (k=6), three trials used 2 mg tablets, one trial used a 1 mg lozenge, and two trials used 2 mg or 4 mg lozenges. Doses were allotted according to participants' dependence levels or time to first cigarette of the day. Nine of these trials compared combinations of two forms of nicotine treatment with only one form and five trials directly compared a NRT product with bupropion SR. In terms of the treatment settings, 69 of the 150 trials included members of the community who volunteered in response to media advertisements who were treated in clinical settings. Twenty three trials were conducted in a primary care or similar setting in which smokers were typically recruited in response to a specific invitation from their doctor. The remaining trials were conducted in antenatal clinics, specialized smoking cessation clinics, hospitals, or in settings designed to resemble OTC use of NRT.

Considering any form of NRT compared with placebo or no NRT, the pooled risk ratio (RR) for abstinence was 1.60 (95% CI, 1.53 to 1.68; I^2=30%; k=117; n=51,265) at 6 months or more followup (**Table 4**; **Appendix F Figure 1**). Overall, 17.3 percent of participants who received some type of NRT achieved abstinence at 6 months or longer (range 2.9% to 60.0%), compared with 10.3 percent of control participants (range 1.1% to 46.0%). All forms of NRT, including choice of NRT, significantly increased the rate of smoking cessation compared with placebo or no NRT. No significant differences were found between the different NRT products through meta-regression. Six included trials[155-160] directly compared different types of NRT (e.g., patch versus nasal spray) and none found statistically significant differences in quit rates. Biochemical validation of self-reported quitting was used in almost all trials (87%). The main findings were not sensitive to excluding trials that did not attempt to validate self-reported cessation. Twenty-five of the 117 trials in the main analysis did not have matched placebo control; however, the findings were not sensitive to the exclusion of these studies.

Nine trials that compared the use of two types of NRT with use of a single type showed a statistically significantly greater cessation effect in pooled analysis (RR 1.34 [95% CI, 1.18 to 1.51]; I^2 =34%; n=4,664) (**Table 4**; **Appendix F Figure 2**). The trials were clinically heterogeneous in the combinations and comparisons used. Two of the trials, one comparing nasal spray and patch with patch alone, and one comparing patch plus lozenge compared with either alone showed a significantly higher rate of continuous abstinence at 1 year with the combined NRT treatment. The other seven trials generally favored combined NRT use versus single form NRT, though they were not statistically significant.

Two studies included within the Stead (2012a) review[140] reported the direct effects of the combination of NRT and bupropion SR versus placebo. Jorenby and colleagues[161] compared quit rates among those randomized to nicotine patch plus bupropion SR with those receiving placebo and found a nearly 4-times greater quit rate among those receiving NRT and bupropion SR (RR: 3.99 [95% CI, 2.03 to 7.85]; n=405). The study by Piper and colleagues[157] did not identify a difference between those receiving NRT lozenge and bupropion SR (n=262) versus placebo (n=37) (RR: 1.54 [95% CI, 0.81 to 2.90]; n=299).

Indirect comparisons of studies based on the type of setting in which smokers were recruited or treated showed that relative rates of abstinence were similar across settings. The pooled RR for trials conducted in primary care was 1.52 (95% CI, 1.34 to 1.71; I^2=9%; k=23, n=11,705). Quit rates among the control groups, however, differed by setting. The lowest quit rate, for example, was found in a trial that provided community volunteers treatment in an OTC setting (2.1%). The highest quit rate (12.1%) was found in a study conducted in smoking clinics. Control-group quit rates were 5.7 percent in primary care settings, 9.5 percent in community volunteers receiving treatment in a medical setting, and 10 percent in those receiving care in hospitals.

The Stead (2012a) review[140] also provided data on indirect and direct comparisons for subgroups based on the level of behavioral support provided to all participants and the dose, duration, and scheduling of nicotine gum and patch. Relative risk estimates were similar across subgroups receiving low-intensity support, high-intensity individual support, and high-intensity group support among both the nicotine patch and gum trials. The other comparisons were based on relatively small subsets of studies and were not the primary focus of this review. Despite this, this information may be of interest to specific readers.[140]

Bupropion

We included three reviews that addressed the effectiveness of bupropion SR on smoking cessation (**Table 1**).[121,129,145] Of the three reviews, the good-quality Hughes (2014) review[121] included the most up-to-date (July 2013) and comprehensive evidence on the effectiveness of bupropion SR. As such, we chose to use this review as the basis for the primary evidence. While the inclusion and exclusion criteria for the other two reviews by Mills[129] and Tran[145] were generally consistent with the Hughes review (**Table 2**), neither of these reviews were as comprehensive or up-to-date (**Appendix C Figure 2**).

The Hughes (2014) review assessed the effects of antidepressant medications, including bupropion SR, on smoking cessation rates at followup at least 6 months following initiation of

treatment.[121] We did not include evidence on other antidepressant medications, such as nortriptyline or citalopram, from the Hughes review as they are not U.S. FDA-approved for smoking cessation. For smoking cessation outcomes, the Hughes review required RCTs to compare bupropion SR with placebo or another non-bupropion SR control, or compare different dosages of bupropion SR. The authors excluded trials in which all participants received the same bupropion SR treatment but received different behavioral support.

The Hughes review (2014)[121] included 66 studies that evaluated the effects of bupropion SR on smoking cessation (**Table 3**). The majority of trials (77%) were conducted in North America. Twenty-nine of the included trials recruited special populations, such as individuals with comorbid health conditions (e.g., chronic obstructive pulmonary disease, schizophrenia, cardiovascular disease), adolescents, specific racial and ethnic groups (African American, Maori), or those who had previously failed to quit smoking using bupropion SR or NRT.

The main analysis in the Hughes review included 44 trials that evaluated smoking cessation after 6 months or more in those taking bupropion SR versus those taking a placebo or no pharmacotherapy. The pooled risk ratio was 1.62 (95% CI, 1.49 to 1.76; k=44; n=13,728) with little evidence of heterogeneity (I^2=18%) (**Table 4**; **Appendix F Figure 3**). Quit rates ranged from 4 percent to 43 percent (19.7% weighted mean) among those receiving bupropion SR and from 0 percent to 33 percent (11.5% weighted mean) among those in the control groups. There was no statistically significant difference among trials that reported cessation outcomes at 6-months versus 12-months followup. The majority of included studies were based on continuous abstinence measures that were biochemically validated (**Table 4**). Ninety-three percent (41/44) of the trials were placebo controlled. Almost all included studies (43 of 44) randomized intervention participants to the recommended dose of bupropion SR at 300 mg daily (150 mg twice per day). Treatment duration ranged from 7 weeks to 26 weeks. Two studies compared the effectiveness of 300 mg versus 150 mg daily doses and found no differences in quit rates at 12 months.[162,163]

The effects of bupropion SR were found to be similar regardless of treatment or recruitment setting (i.e., community volunteer and individuals recruited from health care settings) in *post hoc* indirect comparisons. Similarly, no difference in cessation effects was evident when comparing trials that included intensive *group-based* behavioral interventions to those that provided intensive *individual-level* behavioral interventions for both the intervention and control groups. None of the three studies that used factorial designs to compare the effects of bupropion SR with varying levels of behavioral support found evidence that the efficacy of bupropion SR varied between lower and higher levels of behavioral support or by type of counseling approach provided (i.e., individual-based cognitive behavioral therapy versus group therapy).[164-166]

Varenicline

We included four reviews that analyzed the effect of varenicline on smoking abstinence (**Table 1**).[120,129,145,154] All four reviews included nearly identical bodies of evidence (**Appendix C Figure 3**). The fair-quality review by Mills (2012)[129] and the good-quality review by Cahill (2012)[154] searched for literature through January 2012 and December 2011, respectively. Given the quality and comprehensiveness of the Cahill review, and the lack of detail on specific

exclusions and lack of forest plots presented in the Mills review, we chose the Cahill review as the primary review. The Cahill review evaluated the effectiveness and adverse events for three nicotine receptor partial agonists (i.e., varenicline, cytisine, dianicline) for smoking cessation. We examined the effects and safety of varenicline alone because the other agents are not FDA-approved.

The Cahill (2012) review included 20 RCTs among adult smokers that evaluated the efficacy of varenicline at least 6 months after beginning treatment (**Table 2**). Fourteen studies were included in the main analysis comparing quit rates among those receiving varenicline versus a placebo or a no varenicline control. A meta-analysis of these 14 studies found varenicline had a statistically significant benefit on smoking cessation at 6 or more months followup compared with placebo. The pooled RR was 2.27 (95% CI, 2.02 to 2.55; I^2=63 percent; k=14; n=6,166) (**Table 4**; **Appendix F Figure 4**) based on biochemically validated rates of continuous abstinence. Quit rates ranged from 14 percent to 47 percent (28.0% weighted mean) among those receiving varenicline and from 4 percent to 28 percent (12.0% weighted mean) among those in the control groups. The statistical heterogeneity (I^2=63%) was reduced to zero and the effect estimate increased to 2.74 (95% CI, 2.37 to 3.18) in a sensitivity analysis that excluded four of five studies that had control quit rates above 20 percent. It is not clear; however, why one study with a control group quit rate of 22 percent remained in the sensitivity analysis. Thus, we emphasize the pooled results for all 14 studies while acknowledging the moderate statistical heterogeneity.

Treatment duration for included studies was 12 weeks in all but one trial, which had a 6 week treatment duration. The majority of studies randomized participants to the standard dose of 1 mg of varenicline taken twice per day, although one study prescribed 0.5 mg varenicline from one to four tablets per day *ad lib* depending on smokers' symptoms. Two studies that compared lower doses of varenicline versus placebo found statistically significant benefit of 1.35 mg daily and 0.5 mg twice daily, compared with placebo.

Combination Pharmacotherapy vs. Monotherapy

Combined NRT vs. single NRT. As stated above, combination NRT (i.e., the use of two types of NRT) was found to be superior to a single form of NRT in nine direct comparisons (RR 1.34 [95% CI, 1.18 to 1.51]; k=9; I^2 =34%; n=4,664) (**Table 4**; **Appendix F, Figure 2**).

NRT plus bupropion vs. NRT. A pooled estimate of 12 studies that directly compared adding bupropion SR to NRT versus NRT alone did not suggest a significant benefit of this combination of drugs versus NRT alone (RR: 1.19 [95% CI, 0.94 to 1.51], though studies were clinically and statistically heterogeneous.[121]

Bupropion plus NRT vs. bupropion. A pooled analysis of four trials[157,159,161,167] found a modest, significant effect favoring NRT plus bupropion SR versus bupropion SR alone (RR 1.24 [95% CI, 1.06 to 1.45]; I^2=57%; n=1,991).[140]

Direct Comparisons of Nicotine Replacement Therapy, Bupropion, and Varenicline

All three of the primary reviews for pharmacotherapy[121,140,154] included trials with direct

comparisons of different tobacco cessation medications. We present the results of those direct comparisons below.

NRT vs. bupropion. Hughes[121] included eight studies that directly compared NRT (different forms) with bupropion SR. The Stead review[140] also evaluated five of these eight studies. Both of these reviews reported no statistically significant difference between these two pharmacologic modalities for cessation rates measured at least 6 months after followup. For example, the pooled effect size of eight trials within the Hughes review that compared any form of NRT to bupropion SR was 0.96 (95% CI, 0.85 to 1.09; I^2=27%, k=8; n=4,086).[121] The Hughes review also (2014) included two studies that compared participants that received two forms of NRT (patch and lozenge) with a control receiving bupropion SR and found slightly more benefit of the two forms of NRT.[157,159]

NRT vs. varenicline. Cahill and colleagues[154] included two open-label RCTs[168,169] that directly compared varenicline with nicotine patch. One was a small trial (n=32) conducted by Tsukahara and the other was a larger trial conducted by Aubin (n=746). Neither study found a statistically significant difference in rates of point prevalence abstinence at 24 weeks between participants receiving varenicline versus nicotine patch. The Aubin trial reported a larger benefit for varenicline over the nicotine patch, although not statistically significant, for biochemically validated continuous abstinence at 1 year.

Bupropion vs. varenicline. The review by Hughes[121] included four studies[170-173] that directly compared the effects of bupropion SR versus varenicline on tobacco cessation. All four studies showed more favorable effects for varenicline compared with bupropion SR, though not all were statistically significant. A pooled estimate of the four trials found a significantly lower rate of quitting with bupropion than varenicline (RR: 0.68 [95% CI, 0.56 to 0.83]; n=1,810).

Combined Pharmacotherapy and Behavioral Interventions

We included one good-quality review by Stead (2012b) that assessed the effect of combining pharmacotherapy and behavioral support for smoking cessation among adults (**Table 1**).[138] This review serves as the primary review for this intervention in adults and includes searches through July, 2012. The review included studies in which control participants could be offered usual care, self-help materials or brief advice on quitting. This support, however, had to be of lower intensity than that given to intervention participants. This review excluded trials where fewer than 20 percent of intervention participants were eligible for or used pharmacotherapy. The review also excluded studies where the control group was systematically offered medications, but did not exclude studies where control participants may have obtained pharmacotherapy from other sources (**Table 5**).

The Stead review (2012b) included 41 trials which enrolled 15 to 5,887 participants. Twenty-three studies had more than 100 participants in the intervention group. About half (21/41 studies) of these studies were conducted in the United States and the majority occurred in or recruited from health care settings, such as primary care clinics (7 studies), a health maintenance organization (1 study), or Veterans Administration medical centers (2 studies) and/or recruited people with specific health conditions (e.g., hospital inpatients (8 studies), surgery patients (4

studies), and those with mild airway obstruction or COPD (3 studies). While the included interventions presented a great deal of variation in the intensity and format of behavioral support, the typical intervention involved multiple contacts with a specialist cessation adviser or counsellor, with most participants using some pharmacotherapy (typically NRT) and receiving multiple contacts. The majority of trials (22/41) offered between four and eight sessions and about a quarter (11/41) offered over eight sessions. Specialized cessation counsellors or trained trial staff delivered most of the interventions. The primary care provider was the main interventionist in only three included studies (**Table 6**).

In meta-analysis that combined 40 of the 41 trials, there was a statistically significant benefit of combined pharmacotherapy and behavioral interventions versus control on smoking cessation at 6 months followup or longer (RR 1.82 [95% CI, 1.66 to 2.00]; I^2=40%; k=40; n=15,021) (**Table 7**; **Appendix F Figure 5**). Average quit rates in these trials ranged from 3 to 50 percent (weighted mean: 14.5%) among participants receiving pharmacotherapy and behavioral support, versus zero to 36 percent (weighted mean: 8.3%) among participants randomized to a control group. The original pooled estimate that combined all 41 studies had considerable heterogeneity (I^2=78%). This heterogeneity was deemed to be attributable to the Lung Health Study, which showed a very strong intervention effect (RR 3.88 [95% CI: 3.35 to 4.50]). The Lung Health Study had a very intensive intervention in which participants received nicotine gum free of charge for 6 months and a group-based 12-session behavioral counseling course. Since all of the subgroup analyses presented within this review excluded the Lung Health Study, and we agree that the intervention is much different than the others being combined, we focused on pooled results excluding this trial.

The pooled effect of combined interventions was higher among 31 studies that were conducted in or recruited participants from a health care setting, compared with eight trials that recruited community volunteers. The results in both settings, however, showed significant benefit (Health care: RR 2.06 [95% CI, 1.81 to 2.34] versus Community: RR 1.53 [95% CI: 1.33 to 1.76]) (Chi^2 test for subgroup difference, p=0.00). There was little evidence that the relative effect of the intervention differed according to participant readiness-to-quit. The subgroup of trials that included participants selected for motivation had a slightly larger effect estimate than the subgroup not selected for motivation, although the confidence intervals overlapped. The review found evidence that those trials that offered more personal contact sessions tended towards larger effects. The subgroup of trials that offered eight or more sessions had the largest estimate (RR 2.09 [95% CI, 1.57 to 2.79]; I^2=43%; k=10; n=1,474), but the confidence intervals overlapped for all four groups (i.e., 0 sessions; 1-3 sessions; 4-8 sessions; more than 8 sessions). The review also found no clear evidence that increasing the total duration of personal contact increased the effect. Post hoc meta-regression found no evidence of effect modification by provider type, level of treatment up-take, or the total minutes of personal contact. Indirect comparisons also found little evidence that the relative effect of the intervention differed according to participants motivation or readiness to quit.[138]

Behavioral Interventions Among Adults

We included 26 reviews that evaluated the effects of behavioral tobacco cessation interventions among the general adult population (**Table 1** and **Table 5**).[100,102-104,106,108,111-114,118,119,122,124,131,132,

[136,137,139,141,142,144,147,148,152,174] All 26 reviews that were included in the overall "Behavioral" population-intervention category are further subcategorized into nine groupings:

1. Behavioral Supports as an Adjunct to Pharmacotherapy (1 review)[142]
2. Behavioral Support and Counseling, including counseling techniques such as provider advice, motivational interviewing, or stage-based support (8 reviews)[103,106,108,119,124,131,136,139]
3. Print-Based Self-Help Materials (1 review)[118]
4. Telephone Counseling (2 reviews)[141,147]
5. Mobile Phone-based Interventions (1 review)[152]
6. Computer-based Interventions (6 reviews)[104,111,113,122,132,137]
7. Biomedical Risk Assessment (1 review)[102]
8. Exercise (1 review)[148]
9. Complementary and Alternative Therapies, such as acupuncture and hypnotherapy (5 reviews)[100,112,114,144,151]

There was considerable overlap in the included studies within groupings (i.e., within the eight reviews on behavioral support and counseling) and between intervention categories (i.e., behavioral support and counseling *and* telephone counseling) in terms of the included bodies of evidence (**Appendix C Table 1**). Within each of the nine subgroups of behavioral interventions, we identified one or more reviews that included the most comprehensive and up-to-date literature base and the highest quality to serve as the primary review. Some groups required more than one primary review to represent the breadth of relevant findings. **Table 5** lists the inclusion and exclusion criteria for all 26 included reviews (plus the review by Stead [2012b][138] above) arranged by intervention group, as described above.

Behavioral Interventions as Adjuncts to Pharmacotherapy

Stead (2013a)[142] assessed the effect of increasing the intensity of behavioral support among smokers using smoking cessation medications. Their last search for evidence was July, 2012. They included RCTs in which adult smokers in both the intervention and control conditions received pharmacotherapy for smoking cessation but they differed by the amount of behavioral support. Participants in the control condition received less intensive behavioral support than participants in the intervention condition, even limited to written information alone. This review excluded trials where both groups received behavioral support of the same frequency and duration but differed in specific content (**Table 5**).

The review included 38 RCTs ranging in size from 69 to over 4,500 participants (**Table 6**). Trial participants reported smoking an average of 5 to 35 cigarettes per day. Seventeen trials recruited participants from a health care setting, health maintenance organization, or cessation clinic, including four studies in primary care. The remaining 21 studies recruited community volunteers. All but three studies recruited individuals who were interested in quitting. Over 70 percent (27 of 38) of trials offered NRT as the only pharmacotherapy; three studies offered bupropion SR; one offered varenicline; three offered bupropion SR or NRT; and two studies provided combination therapy of both NRT and bupropion SR. The two remaining studies randomized participants to nortriptyline (not included in this review).

The pooled RR indicated a relatively small increase in smoking cessation at 6 to 12 months with more intense behavioral support among those using one of these types of pharmacotherapy (RR 1.16 [95% CI, 1.09 to 1.24]; I^2=3%; k=38 [39 comparisons]; n=15,506) (**Table 7**; **Appendix F Figure 6**). Quit rates were relatively high in both intervention (weighted mean: 21.4%) and control groups (weighted mean: 18.3%), which is not surprising given that both groups were receiving pharmacotherapy. The effect was similar and also statistically significant for the subgroup of studies (k=27) that examined behavioral support as an adjunct to NRT, specifically. Results of the remaining trials among smokers using other non-NRT pharmacotherapies were generally not statistically significant, although a test for differences between subgroups was also not significant. While the majority of studies reported point prevalence abstinence instead of continuous abstinence, the review did not find any difference in the relative cessation effect between these two outcomes at 12 months. However, studies with point prevalence outcomes had, on average, higher quit rates in both intervention and control arms.[142]

The intensity of behavioral support provided to the control group varied from 0 minutes of contact to over 300 minutes of contact, including face-to-face and telephone contact, with a mode of 4 to 31 minutes. Most studies (k=22) provided less than 31 minutes. The majority of trials offered 91 to 300 minutes of contact (12 studies) or over 300 minutes (16 studies) of behavioral support to the intervention group participants. Despite this large range of intervention and control times across studies, and the requirement that intervention groups receive more intensive behavioral support intervention than control groups, the increment between groups in any given study was generally quite small. This review assigned trials to groups based on the planned total duration of contacts, as opposed to delivered, noting that in general using the actual delivered duration would not have changed the intensity category. In nine trials, while the review's authors categorized the intervention and control groups as receiving the same level of behavioral support (because of the discrete categories described above), the control groups actually received less-intense behavioral support. Indirect subgroup comparisons between those receiving fewer or more contacts failed to find evidence of a dose-response effect.[142]

Behavioral Support and Counseling Interventions

We included eight reviews that we classified as general behavioral support and counseling (**Table 1**).[103,106,108,119,124,131,136,139] Each of these reviews had slightly different goals: four focused on behavioral support provided by physicians,[139] nurses,[136] health professionals in general,[103] or that took place in dental settings;[108] one included stage-based interventions;[106] two considered studies that used motivational interviewing;[119,124] and the remaining review included any behavioral intervention that used brief advice, individual counseling, group counseling, or telephone counseling.[131] Most of the reviews had relatively old searches; six of the eight reviews ended their searches between 2007 and 2011 (**Table 5**). Because of this and the overlap in inclusion and exclusion criteria, most of the included studies within these six reviews were included in the more recent reviews by Stead[139] and Rice[136]as well as some of the other primary reviews listed below (**Appendix C Table 1**). Therefore, the two recent, good-quality Stead (2013b) and Rice (2013) reviews that focus on physician and nurse support for smoking cessation serve as the basis for our primary results here.[136,139] Across all eight reviews, behavioral support tobacco cessation interventions were found to be statistically significantly favorable to control groups (e.g., usual care, minimal intervention) in encouraging smoking

cessation at least 6 months after treatment started in pooled meta-analyses. We found no inconsistencies in reported results across reviews.

The primary review by Stead (2013b)[139] summarized evidence on the effectiveness of physician advice in promoting smoking cessation published through January, 2013. This review included RCTs that compared physician advice to stop smoking versus no advice (or usual care), or compared different levels of physician advice to stop smoking. This review defined advice as verbal instructions from the physician with a "stop smoking" message regardless of whether or not information was provided about the harmful effects of smoking. They categorized studies as minimal interventions when advice was provided (with or without a brochure) during a single consultation lasting less than 20 minutes plus up to one followup visit. This review categorized studies as intensive when the intervention involved a greater time commitment at the initial consultation, the use of additional materials beyond a brochure, or more than one followup visit. This review included 42 trials, 26 of which (presenting 28 comparisons) contributed to their main analysis comparing advice with a no-advice or usual care control. The other 16 trials examined the effect of intensive advice versus minimal advice, compared two interventions similar in content or intensity, or compared advice to computer-tailored letters. These studies were included in separate analyses or discussed narratively in the review.

Smokers who were offered cessation advice by a physician had a statistically significant increase in the likelihood of quitting at 6 months or longer compared with smokers receiving no advice or usual care (RR 1.76 [95% CI, 1.58 to 1.96]; I^2=40%; k=28; n=22,239) (**Table 7**; **Appendix F Figure 7**).[139] There were too few trials in the main analysis (36%) to test the effect size when including only trials with complete biochemical validation. Absolute quit rates ranged from 1 percent to 23 percent among intervention participants (weighted mean: 8.0%), and from 1 percent to 14 percent among control participants (weighted mean: 4.8%). The results of the main meta-analyses were not sensitive to exclusion of trials at high risk of bias for any item. When stratified by intervention intensity, both brief advice and intensive advice showed statistically significant increases in quit rates when compared with no advice controls. There was no evidence of an interaction effect between strata (p=0.31). Direct comparisons, however, between intensive and minimal advice in 15 trials suggested a statistically significant advantage of more intensive advice (RR 1.37 [95% CI: 1.20 to 1.56]; I^2=32%; k=15; n=9,775). Subgroup analyses within this group of 15 trials suggested that this effect might be small or nonexistent among smokers *not* selected as having smoking-related disease (10 studies), but the effect might be larger when the intervention is provided to smokers in high-risk groups (based on only 5 trials).

Indirect comparison between subgroups of studies within the main analysis suggested that interventions that included additional followup visits had a slightly larger effect estimate (RR 2.27 [95% CI, 1.87 to 2.75]; I^2=27%; k=6; n=4,510), compared with no advice than interventions delivered at a single visit versus no advice (RR 1.55 [95% CI: 1.35 to 1.79]; I^2=35%; k=18; n=14,675). Five additional included trials directly compared the addition of further followup to a minimal intervention, but were not included in the main analysis of advice versus no advice. None of these five trials individually detected significant differences between groups.

The other primary review, Rice (2013),[136] searched for RCTs of smoking cessation interventions delivered by nurses through June, 2013 (**Table 1** and **Table 5**). Similar to the review of

physician advice,[139] a nursing intervention included the provision of advice, counseling, and/or other strategies to help people stop smoking provided by a nurse. This review used the same definition of what constituted 'advice' as the Stead (2013b) review. These reviews, however defined intervention intensity slightly differently in that the Rice review defined low-intensity interventions as those that provided advice with or without a brochure during a single consultation lasting 10 minutes or less (as opposed to 20 minutes for the physician advice review) with up to one followup visit. The review defined high-intensity interventions as those where the initial contact lasted more than 10 minutes (again, as opposed to more than 20 minutes for physician advice). These high-intensity interventions also distributed additional materials, used additional strategies, and typically included more than one followup visit.

The Rice review (2013) included 49 trials. Twenty-six of these trials recruited participants from primary care, outpatient clinics, or through home health nurse visits. Twenty-two of these studies included high-risk patients, such as those with diagnosed cardiovascular or respiratory diseases, surgical patients, and head and neck cancer patients (**Table 6**). Seven of the studies examined a smoking cessation intervention that was a component of multiple risk-factor reduction interventions conducted among individuals with cardiovascular disease. Thirty-five of these 49 trials contributed to the main analysis that compared a nursing intervention to a usual-care or minimal intervention control.[136] The remaining comparisons were made between two nursing interventions that involved different components, a different number of contacts (11 studies), or were excluded from meta-analyses given incomplete data.

The estimated pooled RR comparing smoking cessation support provided by a nurse with usual care or minimal intervention was 1.29 (95% CI, 1.20 to 1.39; I^2=50%; k=35; n=17,604) (**Table 7**; **Appendix F Figure 8**).[136] The reviewers noted that a series of sensitivity analyses that used a different model for meta-analysis that excluded studies that did not include biochemical validation of self-reported quitting, limited the analysis to studies judged to be at low risk of bias for selection bias, and excluded studies with less than 12 months of followup did not alter the estimated effect greatly, although the confidence intervals often widened due to smaller numbers of trials. There was no evidence of different effects among interventions classified as low- versus high-intensity through visual inspection or statistical interaction testing (**Appendix F Figure 8**).

Print-Based Self-Help Materials

A single review, the Hartmann-Boyce review (2014), assessed the effectiveness of different forms of print-based self-help materials compared with no treatment or other minimal intervention strategies.[118] The review evaluated 74 RCTs (last search April, 2014) of self-help interventions. These interventions were defined as any materials or programs that smokers use to help them quit smoking that was not also substantively supported by health professionals, counselors, or a group. While the review primarily covered print-based materials, these interventions could include self-help provided via audio or videotape. Interventions only providing brochures on the health effects of smoking were not included because they were usually employed as a control condition compared with more substantial written materials. Interventions were categorized as self-help alone if they included a single session of minimal face-to-face contact in order to share the self-help materials whereas interventions were categorized as brief advice plus self-help if a face-to-face meeting included a discussion of the

intervention content. The review excluded interventions that provided more than one advice session in addition to the self-help materials. Additionally, they excluded interventions delivered via the internet and mobile phone, as well as those that included telephone counseling or hotlines as adjuncts to self-help materials because these interventions were covered in separate recently published reviews (which are also included in this review of reviews).

Thirty-four of the included studies evaluated standard nontailored self-help materials alone or as an adjunct to advice compared with no materials or advice alone. Trials within this group varied in other ways that could potentially impact results, such as the amount of face-to-face advice or counseling provided to both the intervention and control groups. A pooled analysis of trials that compared nontailored self-help materials with no self-help found no evidence of an effect (RR 1.06 [95% CI, 0.98 to 1.16], I^2=23%; k=33; n=29,495), regardless of level of contact and support common to both groups (**Table 7**). There was, however, evidence of a significant benefit of tailored self-help materials versus standard or no materials (RR 1.28 [95% CI, 1.18 to 1.37]; I^2=32%; k=32; n=40,890) (**Table 7**). This effect differed by subgroup depending on the level of face-to-face contact both groups received and whether any materials were given to the control group. For instance, no benefit was detected in the subset of 10 trials in which the intervention group received tailored self-help materials and the control group received standard materials, but groups were matched for number of face-to-face contacts. In contrast, intervention participants receiving tailored self-help materials had significantly higher quit rates than control participants receiving no materials at all. Given this body of evidence, it is difficult to conclude a greater effect for tailored self-help materials than nontailored without direct within-study comparisons.

Telephone Counseling and Support

We included two reviews that evaluated the effects of telephone support to assist smokers in quitting that focused on the effect of proactive (i.e., recruiter-initiated contact) and reactive (i.e., smoker-initiated contact) telephone support via quit- or help-lines or other settings (**Table 1** and **Table 5**).[141,147] All 24 trials included in the Tzelepis review were included in the more up-to-date Stead review (2013c). As such, we used the Stead review as primary evidence for this topic.

The Stead review (2013c) included 77 trials that evaluated the provision of proactive or reactive telephone counseling to assist smoking cessation among smokers of any age, including three trials conducted among pregnant women.[141] Trials ranged in size from 40 participants to over 7,000 (median: 820) and 78 percent took place in North America (**Table 6**). This review grouped trials into three broad categories based on the interventions: (1) interventions among smokers who contacted a helpline (15 studies), (2) interventions of proactive telephone counseling not initiated by calls to quitlines (51 studies), and (3) interventions that provided access to a helpline (3 studies). This review considered the eight trials that did not fall within these predefined categories individually. Within the three broad categories, trials were further subdivided based on the level and type of support provided to intervention participants (e.g., further proactive contact by a counselor among callers to a helpline, telephone counseling intensity [frequency, duration]) and control condition (e.g., minimal intervention, brief intervention/counseling) and based on the recruitment method or motivation of participants (i.e., participants with an interest in quitting or nonselective).

Among 12 trials that compared helpline callers receiving multisession telephone counseling with helpline callers who received self-help materials or a single session of telephone counseling, the pooled analysis showed a significant benefit of the additional telephone counseling on smoking cessation after at least 6 months followup (RR 1.41 [95% CI, 1.20 to 1.66]; I^2 not reported; k=12; n=30,182) based on a random-effects meta-analysis (**Table 7**). The pooled result based on the original fixed-effects model indicated substantial heterogeneity (I^2=71%) (**Appendix F Figure 9**). Quit rates ranged from 5 percent to 17 percent in the intervention groups and from 1 percent to 14 percent in the control groups. Three additional trials evaluated interventions that were limited to the initial call to the helpline and were not included in this pooled analysis.

Fifty-one studies (presenting 52 comparisons) that compared an intervention involving proactive telephone counselling that was not initiated by calls to helplines with a control condition also showed evidence of a moderate benefit at 6 months or longer followup (RR 1.27 [95% CI, 1.20 to 1.36]; I^2=42%; k=52; n=30,246) (**Table 7**). Only about one-third of cessation outcomes within this group were based on continuous abstinence measures or were biochemically validated. Heterogeneity was not explained or reduced based on the intensity of support common to the intervention and control groups or by removing the trials among adolescents or pregnant women. Subsets of trials limited to specific groups of studies found significant benefit for the more intensive condition (**Appendix F Figure 10**), including: where the control group received only self-help materials or brief advice; where the intervention group received face-to-face contact prior to telephone support; or those where telephone counseling was an adjunct to the use or offering of NRT. Overall, however, there was mixed evidence of a dose-response effect based on the intensity of the intervention within the 51 trials of proactive telephone counseling. There was no evidence of such an effect in a meta-regression based on the number of intended calls to intervention participants. Subgroup analysis did, however, find that interventions that included two or fewer calls produced no significant pooled effect (RR 1.07 [95% CI, 0.91 to 1.26]), whereas those that offered between three and six (RR 1.32 [95% CI, 1.23 to 1.42]) or seven or more calls (RR1.29 [95% CI, 1.11 to 1.50]) found significant benefit. Within the broader review, the relative effects of the three trials that provided access to a helpline showed mixed results.[141]

Mobile Phone-Based Interventions

One review by Whittaker (2012) identified five RCTs (n=9,100) that included an evaluation of a mobile phone-based intervention (**Table 5** and **Table 6**).[152] This review excluded trials that used mobile phones as an adjunct to face-to-face or Internet-based programs or where the effects of the mobile phone intervention components could not be separated from the effects of a multicomponent intervention. The review reported considerable heterogeneity (I^2=79%) in a meta-analysis of the five trials based on a Mantel-Haenszel fixed effects model. We do not present the pooled results here owing to the small number of trials, analysis methods, and considerable heterogeneity. Three of the five included trials were based on the same general program in which smokers who wanted to quit and owned a mobile phone were recruited via advertising.[175-177] Individuals randomized to the intervention group received automated tailored text messages that included quitting advice and motivational messages to encourage abstinence. Participants received daily messages leading up to their chosen quit day, an intensive month of five to six messages per day after their quit day, followed by a maintenance phase of one message every 2 weeks for a total of 6 months. Two of the three studies detected significant

evidence of an effect of the intervention on smoking cessation.[175,177] The largest trial that was deemed to be at low risk of bias, for example, detected significant evidence of an effect based on biochemically verified continuous abstinence at 6 months (RR 2.14 [95% CI, 1.74 to 2.63], n=5,792).[177] Within this trial, intervention participants received five text messages per day for the first 5 weeks and then three messages per week for the next 26 weeks. The intervention messages were tailored based on demographic and behavioral characteristics reported at baseline. Participants could also communicate with one another via text for peer support. Another RCT recruited participants through a quitline or email invitation and randomized them to one of five conditions: (1) automated tailored internet-based cessation program only, (2) text message program only, (3) both internet and text message programs, (4) choice of the internet and/or text message program, or (5) minimal treatment control.[178] The text message intervention provided advice and motivational messages according to participants' stage of quitting and reported problems encountered in trying to quit. The frequency of text messages varied according to reported stage of quitting and problems encountered. This trial suggested a benefit from the intervention that was not statistically significant. The final trial sent intervention participants text messages which included a web address that led them to short video clips (less than 30 seconds).[179] The intervention included daily messages delivered up until the chosen quit day, then two messages per day after the quit date that decreased in frequency over the course of the 6-month intervention. Participants within this trial were considered highly addicted according to the Hooked on Nicotine Checklist. This study found no evidence of an intervention benefit. Control participants in all five trials received 'usual care' or minimal contact.

Computer-Based Interventions

Six of the included reviews evaluated the effectiveness of computer- or internet-based tobacco interventions on smoking cessation (**Table 1**).[104,111,113,122,132,137] All of these reviews varied somewhat in their inclusion and exclusion criteria (**Table 5**). For instance, one review focused specifically on internet-based interventions targeting young adults[104] and another review included internet-based interventions that had to make use of the interactive nature of the internet.[137] Reviews varied in their required length of followup from more than 1 month to more than 6 months. Despite these differences, in general, the reviews included very similar bodies of evidence, with the exception of the Health Technology Assessment by Chen and colleagues which included a broader evidence base.[111] The Chen (2012) review included any smoking cessation program that used computer, internet, mobile phone or other electronic aids to generate tailored materials, present or deliver information, facilitate communication, or increase recruitment. Most of the Chen included studies were included in our other primary reviews or represented trials with too short followup (e.g., 2 days, 3 months) and so were not considered in any of our primary reviews (**Appendix C Table 1**). Given the quality, comprehensiveness and inclusion of the Civljak review,[113] it serves as the primary review.

Civljak (2013) included 28 RCTs, representing over 45,000 participants, that evaluated an internet-based intervention.[113] Trials ranged in size from 171 to 11,969 participants. This review excluded trials that used the internet solely for recruitment or to remind participants of appointments for treatment and not for delivery of smoking cessation treatment (**Table 6**). Twenty one of the 28 studies recruited participants via the internet or other advertisements. As such, smokers in most of these trials were motivated to quit and chose to access the internet as a

cessation tool. The included studies tested a variety of interventions, including very low-intensity interventions that provided a list of websites for smoking cessation and high-intensity interventions that comprised internet-, email-, and mobile phone-delivered components. The Civljak review originally grouped the trials into four categories based on the intervention and control conditions (i.e., internet intervention versus nonactive control; internet intervention versus active control; addition of internet as an adjunct to an existing behavioral intervention; one internet intervention versus another internet intervention). Given the substantial-to-considerable statistical heterogeneity found in pooled analyses, they conducted *post hoc* subgroup analyses to inform regrouping trials according to the type of intervention (i.e., interactive and/or tailored internet plus other behavioral components; interactive and/or tailored internet only; or interactive but not tailored internet) and control (i.e., nonactive control [printed self-help or usual care]; active noninternet control [more intensive than self-help such as phone counseling]; or another internet intervention). Given the small number of studies within each comparison, we present the results of Civljak narratively and have created a descriptive forest plot to display the results of each individual trial (**Appendix F Figure 11**). Three studies found a statistically significant benefit for interventions that combined an interactive and tailored internet-based smoking cessation component with telephone counseling or email contact versus self-help materials. Three additional studies all found favorable effects of an interactive and tailored intervention alone compared with a nonactive control. Only one of these effects was statistically significant and all were considered to be of high risk of bias. None of the studies that compared interactive and/or tailored internet interventions with or without other behavioral or pharmacotherapy components with active controls found statistically significant differences. For instance, the study by Swan and colleagues included three intervention groups (IG): (IG1) up to 5 proactive telephone-based counseling calls; (IG2) interactive, tailored online intervention; and (IG3) a combination of arms 1 and 2. This study found nonsignificant effects when comparing IG1 with IG2 and when comparing IG3 with IG1.[180] Three studies with at least 6-month cessation outcomes compared an interactive and/or tailored intervention with an internet intervention that was neither tailored nor interactive. None of the three found a statistically significant benefit of the interactive and/or tailored intervention. Thus, findings for the benefit of interactive and/or tailored interventions compared with less specific interventions were mixed.

Biomedical Risk Assessment

We identified one good-quality review, Bize (2012), that evaluated the efficacy of biomedical risk assessment (with or without other behavioral counseling) to aid in smoking cessation.[102] Biomedical risk assessment interventions included a physical measurement to increase motivation to quit smoking, such as exhaled carbon monoxide (CO), spirometry, atherosclerotic plaque imaging or genetic testing. This review identified 15 trials (presenting 16 different interventions) that met inclusion criteria. These trials had a total of 8,115 participants (90 to 2,110 participants per study). While the clinical heterogeneity of the interventions and populations generally precluded pooled analyses, this review included a meta-analyses for two different comparisons (CO assessment and spirometry in primary care). We do not present the pooled results here because of the small number of studies pooled for each comparison (2 studies). The forest plot generated by Bize is presented to illustrate individual study results rather than to present pooled effect estimates (**Appendix F Figure 12**).

Of the 16 interventions included in the Bize review, four tested the effect of exhaled CO measurements, four tested the combination of exhaled CO measurement and spirometry, three tested the effect of spirometry alone, two tested the effect of undergoing an ultrasonography of carotid arteries with photographic demonstration of atherosclerotic plaques when present, and three tested feedback about genetic susceptibility to cancer (**Table 6**). Among the 15 studies, only two trials detected statistically significant benefit of biomedical risk assessment. The trial by Parkes and colleagues found a significant benefit on biochemically validated point prevalence abstinence at 12 months from a spirometry intervention where participants were given immediate feedback and an explanation of their results in the form of 'lung age' compared with their actual age. This was compared with control participants who were given their spirometry results via a letter and no mention of their lung age.[181] The trial by Bovet and colleagues reported a relatively large effect with a wide confidence interval suggesting no benefit to large benefit comparing an intervention group that received ultrasonography of carotid and femoral arteries and counseling (n=74) with a control group who received counseling only (n=79).[182] Smokers in the intervention group who were found to have one or more plaques identified were given photographs of their plaques with an explanation on the general significance of plaques and their impact on health. These results were based on 7-day point prevalence abstinence at 6 months. The lack of an effect in other studies could be due to an ineffective intervention, overall or in the population recruited, or to limited power, since most studies were relatively small.

Exercise

We included one fair-quality review, the Ussher (2014) review, that evaluated whether supervised or unsupervised exercise-based interventions alone, or combined with smoking cessation interventions, were more effective than a smoking cessation intervention alone.[148] This review included 20 trials that met their inclusion criteria (**Table 5**). While sample sizes ranged from 20 – 2,318 participants, nearly half (8/20 trials) had fewer than 30 participants in each treatment group. Additionally, nine trials were limited to women and one was limited to men (**Table 6**). In all but two trials, participants in both the intervention and control groups received multi-session cognitive behavioral counseling. Seven trials included NRT as part of the smoking cessation intervention and four trials promoted the use of medications. The review reported that none of the included trials showed a significant benefit of exercise on smoking abstinence at 6 months or longer followup, although 13 of the 20 studies showed nonsignificantly higher rates of abstinence among the exercise plus smoking cessation intervention conditions, compared with the smoking cessation intervention conditions. The review's authors note several limitations of the included trials, including the fact that most trials were not sufficiently powered to detect differences between groups.

Complementary and Alternative Therapies

We included five reviews that examined the effectiveness of complementary and alternative therapies on smoking cessation – including three reviews on acupuncture or acupressure,[112,114,151] one review on hypnotherapy,[100] and one encompassing all alternative therapies[144] (**Table 1**). The most up-to-date good-quality review, the White review (2014), served as the primary review for acupuncture-based approaches.[151] We used the Barnes review (2010) as the primary review for hypnotherapy.[100] While the three other reviews included similar bodies of evidence, they were

not as recent as our primary reviews and were of a lesser quality (**Appendix C Table 1**). The White review included 38 RCTs that compared the effects of acupuncture (23 studies), acupressure (five studies), laser therapy (three studies), and electrostimulation (seven studies) versus no or sham intervention for smoking cessation at short-term (six weeks or less) and long-term (6-12 months) followup (**Table 6**).[151] This review reported a positive effect for acupuncture compared with sham acupuncture on short-term cessation (RR: 1.22 [95% CI, 1.08 to 1.38]; I^2=46%; k=16; n=2,588) but failed to find a pooled effect on longer term outcomes (RR: 1.10; [95% CI, 0.86 to 1.40]; I^2=23%; k=9; n=1,892) (**Table 7**). Similarly, there was no evidence of a benefit of acupressure, continuous auricular stimulation, or electrostimulation versus sham interventions on long-term cessation.

The Barnes review assessed the evidence surrounding the effectiveness of hypnotherapy for smoking cessation and included 11 trials indexed through July, 2010.[100] Sample sizes of the included studies ranged from 20 participants to 286 participants. Given the clinical heterogeneity of intervention and control conditions in the body of evidence, this review grouped the studies into comparisons according to the control conditions (i.e., wait list/no intervention; brief intervention; counseling intervention; rapid/focused smoking; drug; placebo drug; or other treatment). The studies varied greatly in the method of hypnotic induction and the number and duration of hypnotherapy sessions they used. In general, this review found no evidence of a difference in smoking cessation at 6 months or greater followup among trials that compared hypnotherapy versus no intervention or other smoking cessation interventions.

Tobacco Cessation Interventions Among Specific Adult Subpopulations (Not Including Pregnant Women or Those With Mental Health Conditions)

Within the 54 included reviews, seven reviews synthesized evidence on pharmacotherapy and/or behavioral tobacco cessation interventions among specific subpopulations of adults: one review concentrated on smokeless tobacco users,[115] four reviews focused on cessation interventions for racial and ethnic minority groups,[109,123,126,134] one only included results for young adults,[150] and one focused on interventions among older adult smokers[153] (**Table 1** and **Table 8**). We summarize the results of each review for specific subpopulations. None of these reviews were considered primary reviews.

The good-quality Ebbert review (2011) included 25 RCTs (presenting 27 comparisons) that examined the effectiveness of pharmacotherapy (11 trials) or behavioral tobacco cessation interventions (14 trials) among users of smokeless tobacco products (e.g., moist snuff, chewing tobacco, Swedish snus, Asian Indian smokeless tobacco products such as gutkha and pan masala) with evidence included through October, 2010. Eleven trials compared a specific pharmacotherapy with a placebo for the effect on all-tobacco or smokeless tobacco abstinence. Two small trials of bupropion SR did not find an effect on continuous all-tobacco abstinence at 6 months. Similarly, there was no effect of NRT including gum, patch and lozenge on smokeless tobacco abstinence (3 studies) on all-tobacco abstinence (5 studies). One study of 431 Swedish snus users reported a statistically significant benefit of varenicline for 12 weeks on biochemically validated continuous all-tobacco abstinence at 6 months, versus placebo (odds ratio [OR] 1.6 [95% CI, 1.08 to 2.36]). Among the 14 behavioral intervention trials, the review found high heterogeneity including by how participants were recruited, the motivation to quit

among the sample, and the additional intervention components, such as the inclusion or not of an oral examination or telephone support. Thus, the trials were not amenable to pooling and had mixed results individually. Seven studies showed statistically significant effects, five showed nonsignificant trends toward a benefit, and two studies presented odds ratios just below one and relatively narrow confidence intervals.

Four reviews[109,123,126,134] focused on tobacco cessation interventions among racial and ethnic minorities (**Table 8**). Two similar reviews, the Liu review (2013)[126] and Nierkens review (2013),[134] examined the effectiveness of U.S.-based smoking cessation interventions that explicitly included cultural adaptations for ethnic minority smokers. The Liu review (k=28, last search April, 2013) reported mixed evidence regarding the effectiveness of adapted versus nonadapted interventions on smoking outcomes, whereas the Nierkens review (k=5, last search April, 2010) reported statistically significant benefits of culturally adapted interventions on smoking cessation in four out of five included studies. Both reviews concluded there was greater acceptability of the culturally adapted interventions, but that more evidence was needed on the effectiveness on smoking cessation, including the benefits for deep- versus surface-structure adaptations. The Carson review (2012) and Johnston review (2013) both specifically examined the effectiveness of interventions for smoking cessation in Indigenous populations.[109,123] All but one of the included studies in both reviews, however, were relevant only to indigenous people in New Zealand (Maori) and Australia (aboriginal peoples). The Carson review included one cluster-randomized study[183] targeting urban health clinics that served American Indians. This study found statistically nonsignificant effects of a culturally-tailored staff training intervention on point prevalence smoking abstinence at 6 months.

Subpopulations based on age were the focus of the Villanti review (2010)[150] and Zbikowski review (2012),[153] which examined the effect of pharmacotherapy and behavioral interventions among younger (18-24 years) and older (50 years or older) adults, respectively. The Villanti review included 14 studies that evaluated behavioral cessation interventions targeting young adults who were moderate-to-high smokers. While the review located no studies of pharmacotherapies in young adults, the last search date for this review was August 2009. Of the 14 included studies, only two had significant results at 4–6 months. One of the studies included 20 weekly visits to a website that provided personalized smoking cessation messages and weekly emails from peer coaches and was also included in the primary computer-based interventions review by Civljak. The other successful intervention included self-help booklets plus telephone counseling provided to those calling a quitline. This study was also included in the Stead (2013c) telephone counseling review. The Zbikowski review reported that nine out of 13 included studies reported statistically significant effects of behavioral and/or pharmacotherapy interventions on smoking cessation at 6 months or more followup among adults aged 50 and older. The review concluded that more intensive interventions and interventions with combined approaches (pharmacotherapy and followup counseling) achieve the best outcomes. The quit rates from their included studies and the relative effectiveness of the specific interventions are consistent with the evidence on smoking cessation in the general adult population.

Electronic Nicotine Delivery System Interventions Among Adults

Based on a search for primary evidence and a review of 25 full-text articles (**Appendix B Figure**

2), we identified two RCTs that evaluated the effectiveness of using e-cigarettes to help current conventional smokers stop or reduce smoking (**Table 9**). In the largest fair-quality trial, conducted in New Zealand, Bullen and colleagues randomized 657 smokers interested in quitting to one of three interventions: 16 milligram (mg) nicotine e-cigarette, 21 mg nicotine patch, or placebo e-cigarette.[105] The method for receiving the respective interventions differed: those randomized to one of the e-cigarette arms were directly mailed the e-cigarette, a spare battery and charger, cartridges, and simple instructions on how to use the e-cigarette whereas those randomized to receive a patch were mailed cards and vouchers to redeem a patch from community pharmacies. All participants were also offered telephone-based support via a quitline which called them directly; participants who declined or did not call back were still able to access other quitline support such as text-messages. At 6 months, there were no significant differences in biochemically verified continuous smoking abstinence between groups. Tobacco smoking cessation was generally low in all three groups: 7.3 percent with e-cigarettes, 5.8 percent with nicotine patches, and 4.1 percent with placebo e-cigarettes. Adherence to treatment was significantly higher in the nicotine e-cigarette and placebo e-cigarette groups compared with the patches ($p<0.0001$) at each follow-up assessment. In addition, 29 percent of non-quitters still used e-cigarettes at 6 months, although it was unknown whether they were using nicotine or non-nicotine cartridges. There was also differential loss-to-followup between groups with only 73 percent of those assigned to the patch retained at 6 months versus 83 percent and 78 percent of those randomized to the nicotine and placebo e-cigarette groups with followup data at 6 months, respectively.

In another fair-quality RCT conducted in Italy by Caponnetto and colleagues, 300 conventional smokers who were not intending to quit were randomized to receive one of three e-cigarette nicotine cartridge doses for the *Categoria* brand model 401 e-cigarette: 7.2 mg nicotine for 12 weeks; 7.2 mg nicotine for 6 weeks followed by 5.4 mg nicotine for 6 weeks; or cartridges with no nicotine. The appearance of the cartridges were identical to maximize blinding; although it is unclear whether allocation was concealed. After the 12-week intervention phase participants were free to purchase e-cigarettes on their own. At 52 weeks, biochemically verified quit rates were borderline statistically significantly different ($p=0.04$) between participants in both nicotine groups (11%) and those receiving no nicotine cartridges (4%). There was no between-group difference in the median number of cigarettes smoked per day at any followup time point.[107] The study did not report whether there was blinding of outcome assessors. In addition, there was substantial loss to followup with 36 percent of those randomized to one of the nicotine-containing cartridges and 45 percent of those receiving non-nicotine cartridges without 12-month followup data.

Key Question 3. What Adverse Events Are Associated With Tobacco Cessation Interventions?

Pharmacotherapy Interventions Among Adults

We included seven reviews that reported adverse events related to pharmacotherapy interventions for smoking cessation in general adult populations (**Table 1** and **Table 2**).[120,121,128,130,135,145,154] Of the six reviews that evaluated the efficacy of pharmacotherapy, two did not systematically review harms of the interventions.[129,140] Mills published two separate reviews: one

specifically on cardiovascular (CV) adverse events related to NRT, bupropion SR, or varenicline (Mills, 2010)[130] and one on any adverse events related to NRT (Mills, 2014).[128] One additional review, the Prochaska review (2012), focused specifically on the risk of CV events associated with varenicline.[135] We discuss the results for all reviews that reported harms for each form of pharmacotherapy individually.

Nicotine Replacement Therapy

The most recent review of harms, the Mills review (2014), included all RCTs reporting CV adverse events within trials evaluating NRT, bupropion SR, or varenicline for tobacco cessation (**Table 2**).[130] The review categorized CV events into two categories: (1) any CV event which included any clinical diagnoses of a CV event including minor events such as palpitations, bradycardia, and arrhythmia) and (2) major adverse CV events as defined by the FDA as a combined outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. For NRT among non-high-risk adults, pooled results suggested a statistically significant increased risk of any CV event among those randomized to NRT compared with placebo (RR 1.81 [95% CI, 1.35 to 2.43]; I^2=0%; k=21; 11,647) (**Table 10**). When restricted to major adverse CV events, pooled results did not clearly establish harm (RR 1.38 [95% CI, 0.58 to 3.26]; I^2=0%). The confidence interval was quite wide, however, and incorporated potential benefit as well as significant harm. As such, this issue deserves further study. A sensitivity analysis found that the treatment effects were driven predominately by more minor CV events, including tachycardia and arrhythmia, and occurred primarily in studies with longer followup periods. The direction of effects was similar among trials of high-risk patients (three studies), although neither outcome (all CV events or major CV events) reached statistical significance.

The second Mills review (2010) examined the relative rate and prevalence of physical and mental adverse events, including life-threatening adverse events, within 92 RCTs comparing NRT with a non-NRT control (e.g., placebo, usual care) and 28 observational studies (**Table 2**).[128] The review pooled RCTs reporting similar adverse event outcomes and estimated odds ratios (as opposed to risk ratios as presented in most other included reviews) for the risk of each event related to NRT. Pooled results found an increased risk of NRT versus non-NRT control for heart palpitations and chest pains; nausea and vomiting (particularly among non-NRT patch users); gastrointestinal complaints; and insomnia. There was no statistically significant increased risk of headache, dizziness, anxiety or depression, or mortality. An increase in skin irritations was specifically related to use of the NRT patch. Mouth and throat soreness, mouth ulcers, and hiccoughs were related to use of oral NRT. Eight studies reported on mortality and did not find a significant association between NRT and controls (OR 0.74 [95% CI, 0.33 to 1.67]; I^2=0%; n=2,765) (**Table 10**). While the Mills review (2010) reported that 25 RCTs reported serious adverse events and indicate that none found a significant increase in serious adverse events with NRT, they do not present the data. As such, we cannot draw definitive conclusions.

Bupropion

The Mills (2014) review suggested no significant increased risk of any CV event for bupropion SR versus placebo (RR 1.03 [95% CI, 0.71 to 1.50], I^2=0%; k=27; n=10,402) (**Table 10**). The confidence interval of the pooled estimate was wide and consistent with a mildly beneficial or

mildly harmful effect. While the results for major CV events were imprecise due to small numbers of events, they were consistent with a possible protective effect or very minor harms (RR 0.57 [95% CI, 0.31 to 1.04]; I^2=0%; k=27; n=10,402) (**Table 10**).[130] When restricted to the eight trials of high-risk patients, the results were in the same direction as non-high-risk adults, but were not statistically significant.[130]

The Hughes review (2014) examined serious adverse events reported in 33 trials of bupropion SR versus placebo or no pharmacotherapy control.[121] This review included studies that were not included in their efficacy analysis because of short followup (i.e., less than 6 months). Serious adverse events were defined per the FDA as any event that was life-threatening, resulted in hospitalization, death, disability, or permanent damage, or required intervention to prevent one of the above outcomes reported during or within 30 days of drug treatment. This review found a nonstatistically significant increased risk in the rate of serious adverse events while on treatment among those randomized to bupropion SR versus control (RR 1.30 [95% CI, 1.00 to 1.69], I^2=0%; k=33; n=9,631), with serious adverse event rates of 2.1 percent for bupropion SR users and 1.9 percent for placebo users or non-bupropion SR participants (**Table 10**). The review found no difference between groups in terms of psychiatric serious events (RR 0.60 [95% CI, 0.28 to 1.28]; k=19; data not shown) or cardiovascular serious events (RR 1.16 [95% CI, 0.65 to 2.06]; k=25; data not shown). The review reported 10 cases of seizures within seven trials that comprised between 100 and 502 individuals receiving bupropion SR (over 13,000 total participants). The review reports this event rate is similar to the rate of 1:1,000 seen in observational evidence and found in product safety data.

Varenicline

Within the Mills (2014) review, among 18 RCTs comparing varenicline with placebo, there was no evidence of an increased risk of any CV adverse events (RR 1.24 [95% CI, 0.85 to 1.81], I^2=0%; k=18; n=9,072) or major CV adverse events among adults (RR 1.44 [95% CI, 0.73 to 2.83]; I^2=0%; k=18; n=9,072) (**Table 10**).[130] The Prochaska review (2012) included 22 double-blind placebo-controlled trials and found a pooled absolute rate of cardiovascular serious adverse events of 0.63 percent (34/5431) for the varenicline group and 0.47 percent (18/3801) for the placebo group. The risk difference and relative risk, however, were not statistically significant.[135] The pooled risk difference was 0.27 percent (95% CI, -0.10 to 0.63; I^2=0%) **(Table 10)**. This review also included relative estimates of risk based on studies with at least one event for comparison and reported a risk ratio of 1.40 (95% CI, 0.82 to 2.39; I^2=0%). Most of the 22 included trials included individuals with current (2 studies) or past (11 studies) CV disease. Six of the 22 included trials were not included in the Mills 2014 review and, as such, these reviews represent somewhat different bodies of evidence.

In addition to synthesizing the evidence on the effectiveness of varenicline, the Cahill review also recorded any adverse effects of varenicline treatment.[154] Nonfatal serious adverse events were reported in 19 of the 20 included trials and a meta-analysis of 17 of these trials (excluding two trials that were not placebo controlled) found an increased risk of one or more serious adverse event among those receiving varenicline, compared with placebo, excluding events that occurred post-treatment (RR 1.36 [95% CI: 1.03 to 1.81]; I^2=0%; k=17; n=7,725) (**Table 10**). This estimate was based on simple counts across the trials that reported one or more adverse

event from participants and does not distinguish between events attributed to or those unrelated to treatment, or between those occurring during the treatment and followup periods. There were no treatment-related deaths in any of the interventions groups during treatment or followup.

Post-marketing surveillance has led to additional safety concerns related to depressed mood, suicide ideation, and suicide behavior concerning both bupropion SR and varenicline. For varenicline, experts have also raised drug safety concerns related to cardiovascular events. We present FDA-issued communication regarding both medications in the Discussion chapter.

Combined Pharmacotherapy and Behavioral Interventions

The one included review on combined pharmacotherapy and behavioral interventions did not report any adverse events related to the interventions.[138]

Behavioral Interventions Among Adults

We examined all 26 included reviews to determine if they measured adverse events related to the interventions. Only two of the 26 included reviews, the Di review and the Barnes review, reported adverse events related to the interventions and both evaluated complementary and alternative therapies.[100,114] The Di review summarized adverse events reported in 13 out of 25 included trials that evaluated the effects of ear-acupuncture, ear-acupressure, and auriculotherapy for smoking cessation. Eight studies reported 115 minor adverse events associated with the intervention (two additional studies did not specify the number of events and another two reported no adverse events). The most reported adverse events from ear acupuncture included sore ears, tenderness, and sensitivity around residual needles, bruising, facial swelling, headache, dizziness, nausea, giddiness, vomiting, euphoria, and insomnia. Adverse events related to ear acupressure included skin allergy to adhesive tape, itchy or sore ear, and discomfort due to ear beads. The remaining study reported that one participant withdrew due to discomfort.[114] The Barnes review looked for reported adverse events among participants taking part in hypnotherapy interventions and found that none of the 11 included studies reported adverse events.[100]

Electronic Nicotine Delivery System Interventions Among Adults

Two RCTs that we included as primary evidence that evaluated the effectiveness of ENDS to aid in quitting smoking conventional cigarettes reported that there were no serious adverse events in either the intervention or control groups related to product use[105] and no differences in the frequency of adverse events among study groups (**Table 9**).[107] The study by Bullen and colleagues found that there was a nonstatistically significant difference in the incidence rate ratio (IRR) for adverse events between these groups (IRR 1.05 [95% CI, 0.82 to 1.34], p=0.7), despite a higher number and proportion of serious adverse events occurring in the nicotine e-cigarette group (27 serious events, 19.7%) than in the nicotine patch group (14 events, 11.8%). The authors deemed none of the adverse events to be related to product use in any of the treatment groups. The study by Caponnetto and colleagues similarly found no difference in the frequency of adverse events among study groups at 12 and 52 weeks. No serious events occurred during the study.[107]

Pregnant Women: Results of Included Reviews

Of the 54 eligible reviews identified for our review of reviews, we included eight that evaluated smoking cessation interventions among pregnant women (**Table 1** and **Table 11**).[92,110,116,119,125,127,133,143] Of these eight reviews, three reviewed both pharmacotherapy and behavioral interventions,[125,127,143] whereas two assessed pharmacotherapy[92,133] and three behavioral interventions alone.[110,116,119] Five reported perinatal health outcomes.[92,110,125,127,133]

Key Question 1. Do Tobacco Cessation Interventions Improve Mortality, Morbidity, and Other Health Outcomes in Pregnant Women?

Pharmacotherapy Interventions Among Pregnant Women

The most recent and comprehensive review on pharmacotherapy for pregnant women is the Coleman review (2012). This good-quality review included six RCTs with last search through March, 2012.[92] All of the interventions included in this review randomized participants to NRT. No trials of bupropion SR or varenicline among pregnant smokers were identified (**Table 12**). The Myung review (2012) was a slightly more recently published review[133] that included only one additional quasi-RCT NRT trial (**Appendix C Figure 4**). This trial did not include a placebo control and was excluded from the Coleman review because there was nonrandom self-selection of participants to NRT, multiple intervention components, and problems with study design that did not permit valid inferences on the effect of NRT alone. The Myung review also was not as comprehensive in reporting as the Coleman review.

Given the small number of trials included in these reviews, the lack of trials of bupropion SR and varenicline, and the time since their last search dates, we conducted a search for primary evidence to bridge the Coleman review (see Methods chapter for details) to the present. We applied the inclusion criteria used in the Coleman review for our study selection. This primary search identified nine full-text studies to review for inclusion and eligibility (**Appendix B Figure 3**). After full-text review, one fair-quality placebo-controlled trial of NRT met the inclusion criteria.[101] Adding this trial to those included in the Coleman review left us with seven trials on the effects of pharmacotherapies among pregnant women included in our review of reviews (**Table 13**).

Within the Coleman review (2012), four of the six RCTs were placebo controlled, as was the additional trial we identified in our primary bridge search.[101] The most common intervention included the use of the NRT patch (four placebo-controlled trials[101,184-186] and one nonplacebo controlled trial[187]). Only two trials used other NRT types—one used gum NRT and placebo gum NRT,[188] and one offered a choice of gum, lozenge, or patch and was not placebo controlled.[189] These trials commonly enrolled women during their second trimester, although one trial enrolled women any time before 27 weeks gestation.[188] The largest study (n=1,050) was the Smoking, Nicotine, and Pregnancy trial (SNAP), which was a multisite RCT of NRT patches conducted in the U.K.[184,190] (The lead author of the primary review for pharmacotherapy in our review of reviews [Coleman] was also the lead author of this trial.) The second largest, and the most recent NRT trial among pregnant women was a multisite trial conducted in France that randomized 402

women to nicotine patches or placebo nicotine patches.[101]

To evaluate health outcomes in pregnant women and neonates, the Coleman review considered RCT studies with control conditions of either no-NRT or placebo. Including the additional study identified in our search, the number of studies available for analyses of each health outcome was low ($k \leq 4$), and did not support quantitative pooling. As a consequence, our review of health outcomes is qualitative. We present forest plots of this data for illustrative purposes only.

Four placebo-controlled trials reported on preterm birth (delivery at <37 weeks gestation).[101,184,185,188] All but the most recent study estimated effects in the direction of a reduced risk for preterm birth with NRT, including the smallest trial, which had a significant result (RR 0.41 [95% CI, 0.18 to 0.94]).[188] This trial was a parallel design RCT allocating 194 currently pregnant smoking women to either 2 mg gum NRT or placebo NRT gum at or before 26 weeks of pregnancy. The remaining three trials had larger samples and estimated nonstatistically significant effects closer to null, ranging from RR 0.85 to 1.03 (**Appendix F Figure 13**). These same trials reported birth weight outcomes, with two finding significantly higher birth weights among women allocated to the NRT arm.[185,188] The largest trials, conducted by Coleman[184] and Berlin,[101] however, did not find evidence of a birth weight benefit (**Appendix F Figure 14**).

Results for stillbirth were inconsistent and the samples and event rates were too small for valid inference. Two of four trials reported slightly more stillbirths in the NRT group, but these trials were underpowered for estimation of the risk of such a rare event (<1%).[184,188] The most recent trial, conducted by Berlin, was also not statistically significant and close to null, but the effect was in the direction of a potential benefit.[101]

None of the included systematic reviews provided evidence on long-term effects of the use of NRT during pregnancy.[184,190] The SNAP trial of NRT during pregnancy included in the Coleman review, however, did recently report two-year followup data.[190] In this trial, just under one-third of participants in each arm completed the 2 year questionnaire. The family physicians of survey nonrespondents were also surveyed. Both study trial arms reported that 88 percent of participants or clinicians completed followup at 2 years, with similar rates of withdrawal and nonresponse between arms over the time period. Comparison group characteristics were similar in the original and followup cohort, including a slightly higher caesarean section rate in the NRT compared with placebo group. This study's authors reported composite variables based on an *a priori* statistical analysis plan. The main outcomes were survival with no impairment (i.e., developmental, neuromotor, sensory) and respiratory problems (i.e., respiratory symptoms, asthma diagnosis, admissions to hospital for respiratory problem). Among respondents with 2 year followup data in the NRT arm (n=445) and placebo arm (n=446), survival with no impairment was significantly higher among those allocated NRT (73% versus 65%; OR 1.41 [95% CI, 1.05 to 1.87]). There was no significant difference in rates of definite developmental impairment (11% NRT, 14% placebo; OR 0.71 [95% CI, 0.48 to 1.06]) between the groups. Multiple imputation intention-to-treat analysis results were nearly identical. For respiratory problems, a five percent observed difference between the arms (30% NRT versus 25% placebo) was not statistically significant (OR 1.30 [95% CI 0.97 to 1.74]).[190]

Behavioral Interventions Among Pregnant Women

We identified six reviews assessing behavioral interventions for smoking cessation during pregnancy.[110,116,119,125,127,143] From these reviews, we chose to use the good-quality Chamberlain review (2013) as the primary review for this topic because it was the most recent and comprehensive.[110] The other reviews of behavioral interventions included fewer studies and their searches were not as recent (**Table 11**; **Appendix C Table 2**).

The Chamberlain review included 86 RCTs and reported intervention effects on health outcomes or tobacco cessation in late pregnancy (**Table 12**). Healthy pregnant women >16 years old were the most common study population, and a majority of studies included women identified as having low socioeconomic status. Most of the included trials recruited women at their first prenatal visit, as long as it occurred before the 3rd trimester. This recruitment strategy ensured these women had enough time to engage in the intervention. Interventions that began in the postpartum period were excluded from the review, but continuing cessation outcomes postpartum were reported in many of the included intervention studies.

Seventy-seven of the 86 trials contributed to the main meta-analysis. The most common intervention was behavioral counseling (k=48). Less common intervention types included feedback (k=7), health education (k=7), incentives (k=4), and social support (k=10) (**Table 12**). Thirty-three of the 77 intervention trials offered multiple interventions (e.g., NRT or self-help video given to both groups with additional intensive counseling given only to intervention group), whereas 31 offered a single intervention. An additional 12 trials used a tailored approach where different intervention components were offered based on an assessment of women's needs and preferences. Usual care was the comparison condition for the majority of trials (k=44), which was generally described as being provided information about the risk of smoking during pregnancy and advice to quit. Thirty-one of the remaining trials used a comparison defined as a 'less intensive' intervention, and two used compared the intervention to an 'alternative' intervention (e.g., cognitive behavioral counseling versus traditional health education). This behavioral intervention review excluded trials comparing efficacy of pharmacotherapy with equal levels of behavioral support.

Some of the intervention trials in the Chamberlain review reported one or more perinatal health outcome. Nineteen trials reported birth weight data. Other, less-commonly reported data included low birth weight (<2500 g) (k=14), preterm birth (<37 weeks gestation) (k=14), stillbirths (k=7), neonatal death (k=4), neonatal intensive care unit (NICU) admissions (k=4), and very low birth weight (VLBW) (<1500 g) (k=3). This review included a sufficient number of studies, with sufficiently low heterogeneity, to obtain results of meta-analysis for mean birth weight, low birth weight, preterm birth, and stillbirth (**Table 14**).

When all 19 studies that reported mean birth weight (including all types of behavioral interventions, with control conditions including usual care or control conditions) were combined, modestly higher mean birth weight favoring the intervention arm was evident (40.78 grams [95% CI, 18.45 to 63.10], I^2=0%) (**Appendix F Figure 15**). The magnitude and significance of the effect was similar when limited to counseling interventions (39.93 grams [95% CI, 9.12 to 70.74], I^2=0%). The magnitude of the mean difference between groups was modest, and there

was some inconsistency in the direction of effects across studies. Evidence of beneficial health outcomes were observed in the pooled analyses across all interventions and comparators for preterm birth and low birth weight (k=14). Pooled effect estimates were similar for these outcomes, with an 18 percent risk reduction for preterm birth before 37 weeks (RR 0.82 [95% CI, 0.70 to 0.96], I^2=0%) (**Appendix F Figure 16**) and a very similar statistically significant estimate for low birth weight (**Appendix F Figure 17**). When restricted to counseling interventions (k=8), while results suggested similar benefits, they were not statistically significant.

Among the seven trials reporting stillbirth, there were no significant differences between study groups and very low event rates and small estimated effect sizes limited precision of estimates. Overall, however, there were slightly more stillbirths recorded in the intervention group compared with the control group (**Appendix F Figure 18**). Three trials of counseling and one trial of a feedback intervention reported on neonatal death, but events were too rare to inform valid conclusions. Similarly, two trials of counseling and two trials of incentive interventions reported on NICU admissions, with half of the trials reporting approximately 25 percent more admissions in the control, compared with treatment arms, and two trials with nearly similar admission numbers between arms (treatment 14/189, placebo 12/189 and treatment 14/30, placebo 13/21 placebo). Two counseling intervention trials and one feedback trial reported on VLBW. While few cases were reported (< 2%), similar rates of VLBW were reported between arms showing slightly more events occurred in the treatment arm in one of the counseling intervention trials.

Key Question 2. Do Tobacco Cessation Interventions Achieve Tobacco Abstinence in Pregnant Women?

Pharmacotherapy Interventions Among Pregnant Women

Meta-analysis of the five placebo-controlled efficacy trials (n = 1,922) showed a nonstatistically significant pooled effect of NRT on biochemically validated smoking cessation at followup (RR 1.24 [95% CI 0.95 to 1.64]), with low heterogeneity (I^2 = 0%) (**Table 15**; **Appendix F Figure 19**). Four of the five studies in this meta-analysis were included in the Coleman (2012) review. We identified the remaining trial through our primary search. Quit rates in these trials ranged from 5 percent to 24 percent in the intervention groups and 0 percent to 15 percent in the control groups (weighted mean 10.8% versus 8.5%). Ignoring one small trial (n=30),[186] the results of the trials were relatively consistent, with effect estimates ranging from 1.08 to 1.27 across placebo-controlled trials in 1,892 women. The review also reported very low rates of adherence to the intervention; particularly in the trials with well-described reporting on compliance, adherence rates less than 25 percent were observed. Including two additional, nonplacebo controlled trials increased the estimate of the pooled effect, but did not alter the statistical nonsignificance of the finding.

With regard to continuation of cessation after pregnancy related to NRT use during gestation, the followup study by Cooper and colleagues[190] found conservatively estimated continuous smoking abstinence rates to be very low—3 percent among NRT users and 2 percent among placebo participants at 2 years, with no statistical difference between groups. Cessation was ascertained

by clinician survey for over half of the trial participants at 2 years. Nonrespondents were assumed to be smokers and included in the denominator. While there were not significant differences between groups earlier in the post-partum period (6 months and 1 year), a significant effect was observed at one year (4% NRT versus 2% placebo) with further adjustment (site, baseline salivary cotinine, partner smoking status, and years completed education).

Behavioral Interventions Among Pregnant Women

The Chamberlain review (2013) identified 60 RCTs and 10 cluster-randomized trials that reported smoking cessation outcomes in late pregnancy, which could include up until hospitalization for delivery (n=21,948). This review included all intervention types, including counseling, health education, feedback, incentives, and social support. Pooled analyses of all behavioral interventions (k=70), regardless of type, including self-reported outcomes, indicated a significant effect of any behavioral intervention on cessation in late pregnancy (RR 1.45 [95% CI, 1.27 to 1.64]), with moderate-to-substantial heterogeneity of estimated effects (I^2=60%) (**Table 15**; **Appendix F Figure 20**). While an overall Chi^2 test for subgroup differences found no difference by the type of intervention (p=0.33), the number of studies varied considerably by intervention type. The results where similar when restricted to trials providing counseling interventions specifically (k=45) (RR 1.37 [95% CI 1.17 to 1.59]; I^2=64%). There was no evidence of a statistically significant effect of social support interventions from analysis of 10 trials that were included in the review (RR 1.29 [95% CI 0.97 to 1.73]). Additionally, the results for some of the less common intervention types were suggestive—pooled effect estimates for financial incentives (k=4) and feedback (k=5) interventions were in a positive direction and included individual studies with statistically significant benefit. Overall test for interaction did not indicate statistical differences among subsets of studies compared according to the number of intervention components.

Biochemical validation of abstinence was conducted in 49 of the trials that reported smoking cessation. The review reported, however, that there was no significant between-group heterogeneity according to whether or not there was biochemical verification (Qb = (1) = 0.06, p=0.80). Nonetheless, observed effect sizes were generally smaller in pooled analyses limited to studies with biochemically validated outcomes.[110] When comparing counseling with usual care and confirming cessation through biochemical validation (k=18), the relative risk for late-pregnancy cessation was 1.25 (95% CI, 1.03 to 1.50) and heterogeneity was lower (I^2=35%).

Key Question 3. What Adverse Events Are Associated With Tobacco Cessation Interventions?

Pharmacotherapy Interventions Among Pregnant Women

As reported in the review of KQ1, we found no evidence of perinatal harms for pharmacotherapy interventions among pregnant women. There were, however, too few studies for pooled analyses, and the available trials were underpowered for assessing rare harms with statistical confidence. As reported above, significant effects of NRT on health outcomes included positive effects identified in individual studies, including higher birth weight in two trials[185,188] and reduced risk of preterm birth in one.[188] The largest trial[184] (n=1,050) reported a significantly higher rate of

cesarean section in the NRT group (20% NRT versus 15% placebo; OR 1.45 [95% CI, 1.05 to 2.01]). The most recent trial, which we identified through our primary search, reported higher rates of cesarean section in the NRT group, but these rates were not statistically different (26% NRT versus 22% placebo; OR 1.21 [95% CI, 0.76 to 1.91]; n=402).[101]

Miscarriage rates were not statistically different (RR 1.24 [95% CI, 0.37 to 4.17], I^2=0%) in the three studies included in pooled analyses in the primary review (n = 1,407). One trial did not adequately describe treatment allocation for seven miscarriages and, as such, was excluded from the analysis. A conservative analysis assuming all miscarriages occurred in the NRT group, however, did not result in a statistically significant difference.

Two large NRT patch trials[101,184] reported detailed maternal and fetal adverse events. These trials reported that the most common adverse event was skin reaction at the patch site, with higher rates in the active NRT patches—nearly 9 percent of NRT users in the Coleman RCT discontinued treatment due to the reaction. The higher rate of Cesarean section in the NRT group was the only serious adverse event difference identified in the Coleman RCT, whose authors cautioned that the low event rates for all adverse events considered do not permit valid conclusions on the safety of NRT during pregnancy. The Berlin trial did not find a significant difference in any fetal outcomes and the Cesarean section rate did not differ by study arm, although there were slightly more cases in the NRT group. Despite having insufficient power to assess the statistical significance of the observed 4 percent difference in having one or more serious maternal adverse event (NRT 12%, placebo 8%), the Berlin trial reported a significant 0.02 mm Hg per day rise in diastolic blood pressure over time in the trial among NRT compared with placebo allocated participants (p=.01). This outcome was not previously reported in trials of NRT in pregnancy.

While stillbirth rates were not significantly different between groups, these events were very rare. In the three studies reporting this outcome,[184,188,189] eight stillbirths occurred in the 733 NRT arm and three occurred in the 669 placebo or no-NRT arm. More events would be necessary for statistical certainty about this outcome and for neonatal death. Three trials reported neonatal death,[184,188,189] where one death was observed in the NRT arms and five in the placebo arms of the three trials (n = 1,386).

Behavioral Interventions Among Pregnant Women

The Chamberlain review[110] noted potential adverse effects of behavioral interventions, including the possibility of a paradoxical effect (i.e. increased smoking), which was observed in the intervention groups of four studies. The review posited that this could occur if exposure to anti-smoking messages motivates resistance to cessation in some participants. This review reported other possible adverse events, including nicotine withdrawal, stigma, and social costs related to peer or partner support, though no trials specifically reported these adverse events as a result of the intervention.

Individuals With Mental Health Conditions: Results of Included Reviews

Of the 54 reviews identified as part of our review of reviews, four assessed pharmacological and behavioral interventions for smoking cessation among individuals with mental health conditions. Of these, two reviews focused on individuals with current or past depression[117,149] and two reviews included people with schizophrenia or schizoaffective disorder (**Table 1**).[99,146]

The good-quality Van der Meer (2013) review provides the primary evidence for depression. This review had a last search date through April, 2013.[149] The review included RCTs conducted among adult smokers with current or past depression that reported at least 6 month followup on cessation outcomes, the majority of which were biochemically validated. A broad definition of depression was employed and ranged from symptoms to diagnosed major depression (current or past). Studies were included regardless of whether depression was identified at study enrollment as a planned design element, or if the study was a subgroup of a trial identified post-hoc (**Table 16**). We also used a review by Gierish (2010) for identification of adverse events as a supplement.[99]

The good-quality review Tsoi review (2013) was the basis of our findings for people with schizophrenia.[146] This review searched for evidence through October, 2012. The review included trials of smoking cessation interventions with at least 6 month followup that were conducted among adult smokers with a current diagnosis of schizophrenia or schizoaffective disorder regardless of their intention to stop smoking. This review did not include trials of individuals with substance misuse disorders. Trials including people with other psychiatric diagnoses where not included in this review unless data for those with schizophrenia or schizoaffective disorder could be isolated. The Banham (2010) review was also examined to identify health outcomes and adverse events.[81]

Key Question 1. Do Tobacco Cessation Interventions Improve Mortality, Morbidity, and Other Health Outcomes in Smokers With Mental Health Conditions?

Individuals With Depression

The Van der Meer (2013) and Gierisch (2010) reviews did not identify any trials reporting health outcomes related to smoking cessation interventions among smokers with current or past depression.[117,149]

Individuals With Schizophrenia or Schizoaffective Disorder

The Tsoi (2013) review included trials of bupropion SR versus placebo that reported mental-state outcomes, including positive and negative symptoms at the end of treatment, as well as depressive symptoms at the end of treatment. This review reported that there was no evidence that smoking cessation treatment with bupropion SR worsened mental health among study participants, but these findings are not robust since the reporting of outcomes varied among

trials. Two trials reported change in positive symptoms, for example, while three trials reported changes in negative symptoms and an additional three trials reported change in depressive symptoms. There was no effect for any of these outcomes within individual studies or in an pooled analysis that included the few studies that reported these outcomes. Similarly, while there was little evidence available for trials of varenicline, no trials reported declines or improvements in mental state outcomes.[146] Likewise, the Tsoi review reported no health outcomes related to behavioral interventions for smoking cessation among patients with schizophrenia or schizoaffective disorder, although it appears that there were measures of mental health status included in most of the trials. The Banham (2010) review reported that there was no change in mental health outcomes (measured using validated tools) in one trial that compared participants assigned to a group American Lung Association intervention compared with participants assigned to a specialized group therapy intervention for smoking cessation among people with schizophrenia or schizoaffective disorder.[81]

Key Question 2. Do Tobacco Cessation Interventions Achieve Tobacco Abstinence in Smokers With Mental Health Conditions?

Individuals With Depression

Among smokers with *current* depression, the Van der Meer review (2013) identified eight trials that tested the efficacy of antidepressants compared with placebo for smoking cessation, all using biochemical validation. Five of these trials tested bupropion SR in smokers with mild depression, two tested fluoxetine, and one tested paroxetine (the latter three studies are not discussed here because our review is limited to trials of drugs explicitly approved by the FDA for smoking cessation) (**Table 17**).[149] Four of the five trials of bupropion SR tested the antidepressant alone compared with placebo, and one trial tested bupropion SR versus placebo with NRT as an adjunct in both arms among smokers with current depression. None of the trials had sufficient power to statistically distinguish observed differences however. The largest trial (n=161) reported fewer people with 6 months abstinence in the intervention group compared with placebo. The remaining four trials (each with n<100) reported higher rates of cessation in the intervention group. Among smokers with *past* depression, four trials (with five comparisons) tested bupropion SR versus placebo (one comparison tested bupropion SR + NRT versus placebo + NRT). The trial that compared NRT as an adjunct in bupropion SR and placebo comparison groups had a statistically significant effect (RR 5.46 [95% CI 1.71 to 17.40], n=87). While the other four trials were not statistically significant, all except one trial reported higher rates of abstinence in the intervention arm. Given the limited trial evidence available, effects of other pharmacotherapies for smokers with current or past depression were unclear. Five trials compared rates of 6-month abstinence from NRT versus placebo among currently depressed (k=1) and previously depressed (k=4) smokers. While all comparisons were generally positive, none had sufficient power to allow for statistical inference.[149]

In terms of behavioral interventions, Van der Meer (2013) identified 49 RCTs that reported cessation outcomes; 33 of them included a mood management component, primarily cognitive behavioral therapy (group or individual), specifically for depression.[149] Among smokers with current depression, adding a mood management component to the standard intervention was beneficial for quitting smoking at 6 months in a pooled analysis of 11 trials (RR 1.47 [95% CI

1.13 to 1.92]; I^2= 0%, n=1,844). Sensitivity analyses in trials of individuals with current depression did not identify factors suggesting group differences based either on trial design or type of support. This conclusion, however was based on a limited number of studies available for comparing subgroup effects across trials. The evidence for a benefit of similar magnitude was also present in smokers with past depression (RR 1.41 [95% CI 1.13 to 1.77]; I^2=23% k = 13, n = 1,496). Studies of other types of behavioral interventions (not including a mood management component) were too heterogeneous to combine in the main analysis and subgroup meta-analysis of these other types of behavioral interventions among smokers with past or current depression was not possible, given limited trial evidence.

Individuals With Schizophrenia or Schizoaffective Disorder

The Tsoi (2013) review included five trials of bupropion SR reporting 6-month followup data on smoking cessation.[146] All trials reported more quit events in the intervention arm, and a significant pooled estimate of effect was reported (RR 2.78 [95% CI 1.02 to 7.58], I^2=0%), but precision is limited because the number of events (18) and overall number of trial participants were very low (n=214).

Of the two trials comparing varenicline with placebo, only one reported 6 month abstinence (n=128). This trial had unclear risk of bias across most quality criteria and was sponsored by the drug company that produces varenicline. Additionally, this trial's results were not statistically significant, despite a five-fold difference in cessation rates.

There were no studies designed to assess the independent effect of NRT with placebo or non-NRT control. Two studies evaluated NRT of differing doses and other studies combined NRT with other interventions. One trial (n=169) combined a counseling intervention with nicotine patches in comparison to usual care, but cessation results were not statistically significantly different at 6-month followup. Another trial compared the effect of contingent reinforcement using financial incentives (with and without the nicotine patch) to a minimal intervention. There were 80 patients in this trial available for subgroup analysis of those with schizophrenia or schizoaffective disorder, and only one-third wished to stop smoking. At followup, beyond 6-months, abstinence was higher in the group receiving the nicotine patch alongside monetary incentives (50%) compared with the incentives without NRT (28%) and the minimal intervention (10%). Biochemically validated abstinence, however, did not differ between arms at followup.

The Tsoi review identified three additional trials that tested behavioral interventions.[146] One compared an American Lung Association program with specialized cessation group therapy for schizophrenia patients (both arms received the nicotine patch). The specialized group-therapy arm had higher reported rates of smoking cessation at 6-months (17.6% versus 10.7%, $p<0.03$). A second trial of behavioral interventions compared two different behavioral counseling approaches that provided nicotine patches to both study arms and found no significant difference in cessation at 6- or 12-months. A third trial compared active repetitive transcranial magnetic stimulation (a noninvasive procedure that can induce changes in brain cortical function with the potential to reduce tobacco craving) with sham repetitive transcranial magnetic stimulation. This trial, however, reported no difference in cessation outcomes at 10 weeks. They did not report outcomes at longer followup time points.

Key Question 3. What Adverse Events Are Associated With Tobacco Cessation Interventions?

Individuals With Depression

The Van der Meer review (2013) did not report on adverse events for the included trials.[149] The remaining systematic review conducted among patients with depression was a less recent, fair-quality review, but provided data on adverse events.[117] Eleven of the 16 included trials in the Giersch review did not report data on adverse events, and only three of the 16 trials provided detailed information on adverse events. The adverse events reported for a trial of bupropion SR that was included in the Van der Meer review included headache, insomnia, dry mouth, and increased anxiety and for a trial of NRT also included in the Van der Meer review, a small proportion of participants reported heart palpitations, nausea, vomiting, dizziness, difficulty breathing, tongue blisters, damage to dental work, and sore jaw. Overall, these reviews did not identify any severe, life-threatening adverse events attributed to pharmacological smoking cessation interventions among people with depression, although data are quite incomplete. There were no adverse events related to behavioral interventions among individuals with depression reported in any of the included reviews.

Individuals With Schizophrenia or Schizoaffective Disorder

The reported adverse events in bupropion SR trials conducted among individuals with schizophrenia were generally not serious. These events included dry mouth, feeling jittery, light-headedness, and frequent night waking.[191] While one patient in the bupropion SR arm of a trial had a seizure, the individual had a preexisting condition determined to precipitate the seizure. No seizures were reported in the other trials.[146] Three of 59 participants in one trial experienced a psychotic break during the trial: one was in the bupropion SR arm and two were in the placebo arm. The trial of varenicline that reported 6-month outcomes had 13 serious adverse events (among 10 trial participants). Nine of these events occurred in the intervention group and one occurred in the placebo group (accidental death during post-treatment followup). The authors attributed two serious suicide-attempt hospitalizations to varenicline use. No adverse events from behavioral interventions were reported for those with schizophrenia or schizoaffective disorder.[99,146]

Chapter 4. Discussion

Summary of Evidence

Behavioral counseling interventions for smoking cessation, with or without adjunct pharmacotherapies, are more completely studied than any other single behavioral health topic. Although often reported in our text as "pharmacotherapy" interventions for brevity, it is important to remind readers that these interventions almost always include some level of behavioral support in addition to the medication. This behavioral support level is often minimal and does not differ between treatment and placebo/control groups. Some trials explicitly examine more robust independent interventions (medications plus robust behavioral interventions). We explicitly identify when the behavioral support is intentionally varied as part of the experimental design.

We conducted a review of reviews approach to update the evidence supporting these interventions for three populations: unselected adults, pregnant adult women, and adults with mental health conditions. This approach allowed us to summarize evidence on health outcomes, cessation outcomes, and harms for three main types of pharmacotherapies (NRT in various forms, bupropion SR, and varenicline), nine categories of behavioral interventions, and various combinations of behavioral and pharmacotherapy approaches from 54 relevant systematic reviews. Twenty two of these provided primary review results for specific population-intervention combinations, with more than 800 RCTs represented. We compared review-level results from the other 32 nonprimary reviews relevant to specific population-intervention groups with results from the primary reviews to confirm overall consistency or to supplement findings (as in the case of harms reporting). We supplemented the review of reviews approach by conducting a primary search for trials evaluating the use of ENDS for smoking cessation given the more recent emergence of this technology. We also conducted a bridge search from the last search date of the primary systematic review to locate all recent primary literature related to pharmacotherapy interventions among pregnant women. As part of our *a priori* review of reviews approach, we specified the conduct of additional primary searching for population-intervention combination such as this one, characterized by a small number of included trials and imprecision in the effect estimate in the primary review.

General Adult Population

Available evidence on health outcomes among general adults represented a single behavioral intervention (physician advice) with no pharmacological treatment (**Table 18**). The research field has largely progressed past this research question, recognizing that the health benefits of smoking cessation are already firmly established.[3,10] The vast majority of studies reported cessation outcomes as primary outcomes and emphasized improved validity through biochemical verification or more stringent definitions of abstinence.

Overwhelming evidence suggests that pharmacotherapy, behavioral, and combined pharmacotherapy and behavioral smoking cessation interventions readily available to primary

care patients and clinicians can increase biochemically verified quit rates in adults at 6 months or longer followup (**Table 18**). Based on research involving almost 50,000 individuals, NRT over 1 to 12 months in all forms was effective and increased relative quit rates (mostly defined as continuous abstinence rather than point prevalence) by 53 to 68 percent compared with placebo or no NRT (RR 1.60 [95% CI, 1.53 to 1.68]). The absolute difference in mean cessation rates between the NRT and control groups was 7 percent (17.3% versus 10.3%). Based on research involving about 13,000 individuals, bupropion SR increased relative rates of biochemically verified cessation by about 62 percent at 6-12 months, defined primarily using continuous abstinence measures (RR 1.62 [95% CI, 1.49 to 1.76]). The absolute difference in mean cessation between the bupropion SR and control groups was 8.2 percent (19.7% for bupropion SR versus 11.5% for controls). A smaller body of evidence (n=6,166) comparing varenicline to placebo found relatively larger effects on smoking cessation (RR 2.27 [95% CI, 2.02 to 2.55]), defined stringently as 100 percent biochemically verified continuous abstinence.

Combination pharmacotherapy may also hold some promise. Combination NRT increased the chance of quitting by more than 30 percent compared with a single form of NRT (RR 1.34 [95% CI, 1.18 to 1.51]). This evidence led to recent changes in FDA-approved OTC NRT labeling allowing for the removal of a warning on using more than one NRT product simultaneously.[30] Additionally, calls have been made for more explicit statements to be added to FDA labels for NRT that state that the use of longer-acting NRT concomitantly with faster-acting NRT is safe and likely improves quit rates among smokers who smoke 10 or more cigarettes per day.[192] In terms of other combinations of drugs, a pooled analysis of four trials found a small, but significant effect favoring NRT plus bupropion SR versus bupropion SR alone; however, adding bupropion SR to NRT versus NRT alone did not suggest a significant benefit in 12 trials. Three recent trials that were not included within our review of reviews found mixed results regarding the effect of combined pharmacotherapy on cessation. Koegelenberg and colleagues reported that the use of varenicline and a NRT patch increased the odds of continuous abstinence at 24 weeks by almost 100 percent compared with varenicline only.[193] In contrast, however, Ramon did not find a significant benefit of varenicline plus a NRT patch versus varenicline alone on continuous abstinence at 12 or 24 weeks.[194] Ebbert and colleagues found slightly higher rates of prolonged abstinence at 6 months among those receiving bupropion SR plus varenicline versus varenicline alone, although this effect was not evident at 1 year.[195]

Combined behavioral counseling interventions and pharmacotherapy (primarily one or more forms of NRT or bupropion SR) also resulted in higher cessation rates compared with brief advice or self-help materials. The pooled estimate from a meta-analysis of 40 combined intervention trials (n=15,021) suggested that combined interventions might increase cessation by 66 to 100 percent (RR: 1.82). In a series of *a priori* subgroup analyses, combined intervention effects were significantly higher in participants from health care settings compared with community volunteers and tended to increase with greater numbers of sessions among interventions with an interpersonal component. No clear evidence was found to support an increased effect for combined interventions with greater total duration of personal contact. A separate review that examined variations in the amount (intensity) of behavioral intervention support in combination with pharmacological interventions among trials in 15,506 general adults found that the incremental effect of additional behavioral support was significant, but small (RR 1.16 [95% CI, 1.09 to 1.24]). Both groups, however, always received the same

pharmacotherapy—mostly NRT, with several trials of bupropion SR and one of varenicline—and the incremental difference in intensity between arms was modest, in the neighborhood of 0.5 to 5 hours difference.

Research on behavioral counseling interventions that include no pharmacologic treatments in adults represent a broad range of approaches. These interventions can range from in-person advice and support from physicians and nurses to a plethora of non-face-to-face formats (tailored and nontailored self-help materials, quitlines, outreach telephone counseling, mobile phone interventions, internet interventions). Compared with various controls, behavioral interventions produced modest improvements in relative smoking cessation at 6 or more months (18%-96%). Physician advice, even brief, resulted in a significant relative improvement in quitting smoking compared with usual care (RR: 1.76 [95% CI, 1.58 to 1.96]). These data suggest that many options can effectively aid cessation and a range may provide options amenable to smokers' preferences. Given the small number of studies and heterogeneous findings, more research is needed on the use of nontailored print materials and mobile phones and in particular, text messaging to aid in cessation. The presence of two relatively large trials that show favorable effects of personalized text messages shows particular promise for this new behavioral approach. Similarly, despite a larger body of existing trials, internet-based interventions that involve a large number of participants seeking to quit and that obtain verified outcomes would be very useful.

Trials in general adults have also examined means to enhance motivation through biomedical risk assessment or to provide additional support during cessation through exercise, acupuncture, and hypnotherapy. Biomedical risk assessment had mixed results representing diverse interventions that could not be combined. Results for exercise, acupuncture, and hypnotherapy were not definitive.

NRT, bupropion SR, and varenicline were not generally associated with an increased risk in serious adverse events among the general adult population, including major cardiovascular (CV) adverse events (**Table 18**). NRT, however, was associated with a higher rate of *any* CV adverse event, although this was largely driven by low-risk events, typically tachycardia (a well-known risk). These reviews suggested a possible protective effect or very minor harm related to major CV events among users of bupropion SR (RR 0.57 [95% CI, 0.31 to 1.04]), but these analyses were based on a small number of events. Varenicline has been less completely studied for benefits as well as harms than NRT or bupropion SR.

Post-marketing surveillance of both bupropion SR and varenicline has raised concerns regarding their safety related to neuropsychiatric outcomes (including suicide ideation and attempts) as well as for serious CV events for varenicline. Labels for bupropion SR include a boxed warning related to increased risk of suicidal ideation and behavior in individuals taking antidepressants and serious neuropsychiatric events among those taking bupropion SR for smoking cessation.[196,197] The FDA issued separate warnings related to varenicline and risk of CV adverse events in 2012[198] and neuropsychiatric adverse events in 2011.[199] The varenicline label currently contains a boxed warning related to serious neuropsychiatric events that may occur while taking varenicline or shortly after discontinuation.[196] A pooled analysis of 17 Pfizer-sponsored placebo-controlled trials of varenicline (n=8,027) did not find an increased risk from varenicline on rates of suicidal ideation or behavior or neuropsychiatric events, however. Additionally, psychiatric

illness was not found to moderate the effect of varenicline safety.[200] While there is no boxed warning for varenicline regarding cardiovascular events, the *Warnings and Precautions* section of the varenicline label includes the results of a meta-analysis that found a nonstatistically significant higher occurrence of major adverse CV events among patients using varenicline, compared with placebo. The FDA is continuing to evaluate the risk of major adverse CV effects through a large safety clinical trial by the manufacturer of Chantix®.[201] Continued monitoring of the safety of varenicline is warranted, particularly for neuropsychiatric events.

We found limited evidence on potential harms related to behavioral interventions with only two reviews synthesizing potential harms – one on ear acupuncture and one on hypnotherapy.

Pregnant Women

Few trials estimated the effects of NRT on infant health outcomes, and our reviews included no trials evaluating other pharmacotherapies (**Table 19**). Three out of four trials reported fewer cases of preterm birth in the intervention arm, however, with one reporting a statistically significant difference. Higher birth weight in the intervention group was found in the two trials, but the two largest trials had null findings. Longer-term child health outcomes (up to age two) were reported based on followup data from the largest trial. Survival with no impairment was higher for the children of NRT-allocated women (73% versus 65%). Thus, the impacts on infant health outcomes with NRT were sparse, somewhat mixed, but generally favoring no harm or slight benefit.

There was evidence of statistically significant infant health benefits from behavioral interventions. The mean birth weight of infants was modestly higher in the intervention group when considered across all types of interventions and when limited to counseling interventions. Consistent with this finding, the risk for low birth weight (< 2500g) and preterm birth were reduced with behavioral interventions. The number of trials reporting outcomes and event rates for stillbirth, VLBW, NICU admissions, and neonatal death were too low to estimate effects with enough precision to draw conclusions.

In terms of the effects of interventions on smoking cessation outcomes, there was considerably more evidence available on the effects of behavioral interventions during pregnancy than for pharmacotherapies (**Table 19**). Based on pooled data from trials among over 20,000 women, behavioral interventions were effective for smoking cessation in late pregnancy (RR 1.45 [95% CI, 1.27 to 1.64]). Although the most common type of intervention was counseling, trials of financial incentive interventions, feedback, social support, and health education had fairly consistent findings of benefit, including some significant individual trials.

In contrast, there was no evidence of NRT efficacy for validated smoking cessation in late pregnancy based on the currently available evidence (five placebo-controlled trials), although all trials reported slightly more cessation events in the intervention group (**Table 19**). The low adherence to NRT reported in the trials hinders interpretation of the available evidence. Benefits and harms from exposure to NRT are more difficult to discern when exposure is limited and variable. Additional evidence is expected in the relatively near future since there are three ongoing trials of NRT and three ongoing trials of bupropion SR for smoking cessation among

pregnant women. There is also one ongoing trial of varenicline and one ongoing trial of bupropion SR investigating the effects of exposure to these therapies on perinatal health outcomes (**Appendix G Table 1**).

In terms of harms related to cessation interventions, among pregnant women, while evidence on the health outcomes of NRT are somewhat reassuring, there was limited power to rule out potential rare harms (**Table 19**). The largest trial of NRT observed higher cesarean section rates for women assigned to NRT compared with placebo (20% versus 15%), and a more recent trial reported a similar, but not statistically significant difference in cesarean section rates (26% versus 22%). While there was no evidence showing differences in rare outcomes such as miscarriage, stillbirth, and neonatal death, these data are limited. A recent NRT trial identified a rise in blood pressure of 0.02 mm Hg per day over the course of pregnancy occurring more commonly in the NRT compared with placebo group (12% versus 8%). This outcome was not assessed in earlier trials. There was no evidence of adverse events related to behavioral interventions among pregnant women.

Individuals With Mental Health Conditions

Among individuals with mental health conditions, we found evidence from reviews on tobacco cessation interventions for individuals with depression and for individuals with schizophrenia and schizoaffective disorder (**Table 20**). There was no evidence on the effects of interventions on health outcomes among adults with mental health issues. For depression, intervention effects on smoking cessation were estimated separately for trial evidence from patients with current depression and those with past depression. Neither group provided adequate trial evidence to draw conclusions from pooled estimates on the efficacy of pharmacotherapy. The most common pharmacotherapy tested for patients with current or past depression was bupropion SR. Effects in individual trials were not statistically significant, with the exception of one trial in patients with past depression that included NRT as an adjunct in both study arms. While effects appeared to be fairly consistent, in a beneficial direction, the lack of precision limits interpretation.

There was far more trial evidence available on the effectiveness of behavioral interventions among smokers with depression. There was evidence of a smoking abstinence benefit at 6 months among current or past smokers with depression with the addition of a mood management component to standard smoking interventions. Results in both populations had low statistical heterogeneity, moderate effect sizes, and adequate precision. Trials of other types of behavioral interventions were too few and were too heterogeneous to allow us to draw conclusions.

We did identify evidence that bupropion SR increased smoking abstinence at 6 months in trials of people with schizophrenia or schizoaffective disorder, but this was based on very few events and few trial participants. There was no evidence on the effects of NRT alone in placebo controlled trials for this patient population. Likewise, three trials of different types of behavioral interventions in this population have also been published, but none provided evidence of a benefit.

The reviews found no severe adverse events attributed to pharmacological smoking cessation interventions among people with depression or schizophrenia, although these data are

incomplete. There were no trials of behavioral interventions that suggested harm among those with mental illness.

Electronic Nicotine Delivery Systems

ENDS are a relatively new product category and none of the specific products have been approved as a cessation intervention by the US FDA. Despite this, knowledge about these nicotine-containing devices may be important for providers who wish to deliver comprehensive tobacco-related counseling to their patients. Our review of two RCTs along with a number of recent systematic reviews[83,84,86,87,89,202,203] generally concluded that available data on the use of ENDS for quitting conventional smoking are quite limited and suggest no benefit on smoking cessation among smokers intending to quit. The most recent systematic review on this subject [204] included the same two trials that we summarized, with neither trials suggesting benefit on smoking at 6 months or more. In addition, neither of these two trials nor a number of observational studies included in the recent review reported any serious adverse events considered to be plausibly related to ENDS use. The paucity of trial data on adverse events related to ENDS use is also part of the ongoing debate regarding the appropriateness of their use as a cessation tool.

Most e-cigarette users believe that e-cigarettes are less toxic than conventional cigarettes.[205] Despite this belief, the toxicity and safety of e-cigarettes cannot be uniformly determined because of the large variation in devices and cartridge fluids available, and the new products rapidly entering the market. Among the brands that have been tested, levels of toxins have been found to be substantially lower than conventional cigarettes, but limited data are available.[66,206,207] While the use of e-cigarettes does not include the inhalation of tar and carbon monoxide, other materials such as metals, plastics, rubber, ceramics, flavors, fibers, and foams that are often used in e-cigarettes can contribute to adverse health effects.[208] Furthermore, the potential harms of long-term e-cigarette use are not known. In young people, concerns include the potential negative impact of nicotine on brain development,[209] as well as the risk for initiating the use of conventional cigarettes or other tobacco products and nicotine addiction. In addition, the nicotine in the e-liquid can be hazardous if mishandled and can be toxic to children. The number of calls to poison centers involving e-cigarette liquids containing nicotine increased from one per month in September 2010 to 215 per month in February 2014.[210] The use of e-cigarettes with illegal substances is also a concern. Patents for the devices acknowledge that with no or slight modification, the device can be used with narcotics, steroids, marijuana, and other substances.[208]

The high rate of dual use of electronic and conventional cigarettes among current e-cigarette users suggests that e-cigarettes are being used to satisfy their nicotine addiction rather than using them as a means for quitting smoking entirely. This is possible because they are allowed in venues where conventional smoking is prohibited. This raises concerns that the public health impact of e-cigarettes as a smoking cessation tool could be minimal whereas widespread e-cigarette use could re-normalize smoking and induce smoking adoption among youth.

Given the variation and current lack of regulatory oversight on the content of e-cigarettes and the limited evidence available from well-designed studies, further research is clearly needed. We identified a number of clinical trials currently under way or planned that address, or will address, the effectiveness and safety of e-cigarettes as a tobacco cessation aid that may be of interest to the USPSTF in the future (**Appendix G Table 2**).

Limitations of the Review

Our review has several limitations, including our review of reviews approach, the methods and quality of the included reviews that synthesized the bodies of evidence, as well as the primary studies themselves.

The comprehensiveness of our review of reviews is inevitably limited by the recency and quality of the source reviews. Although most of the primary reviews that served as the basis for the main results included evidence at least through 2012, there may be evidence on particular population and intervention subsets that have been published after each review's last search date. If this occurred, it could contribute to each respective body of evidence not reflecting these newer studies. Given the consistency of the effects within each group over time, however, we expect that any new trials regardless of their sample size and effect estimates would have little bearing on the overall results of this review of reviews. We identified five published protocols for planned or ongoing systematic reviews related to the effectiveness and/or safety of tobacco cessation interventions (**Appendix G Table 3**). One pending review focuses on the effectiveness and safety of all three first-line pharmacotherapies and/or behavioral interventions among adults; one on combined pharmacotherapy and behavioral interventions among people of all ages; one specifically evaluates the effect of physician advice on smoking cessation, quality of life, and adverse events among people with schizophrenia or related disorders; one only includes adults aged 65 years and older; and the fifth review plans to report neuropsychiatric adverse events related to varenicline. The addition of these reviews, when published, might supplement the results of this review of reviews.

By adopting a review of reviews approach, we relied on the data as described and assessed by the original reviewers. In doing this we trusted that each review generally included the full available and eligible evidence base, that the data abstraction was accurate, and that the analyses were scientifically sound. We used scientific judgment, however, when choosing which reviews to present as the basis for the primary findings and which pooled data were appropriate to present. For instance, although review authors may have presented several pooled analyses based on various subgroups within the main analysis, we carefully chose which data to include in our synthesis based on our *a priori* questions of interest (e.g., type and intensity of intervention, setting and provider, participant selection, and verification of abstinence measures). We did not reassess the risk of bias or quality of individual trials, instead we reviewed the risk of bias as presented in the review and interpreted results in light of these potential biases. Although we did not quality rate the reviews based on the specific choice of meta-analytic models (i.e., random versus fixed effects), we were cautious about reporting pooled results for small numbers of studies or highly heterogeneous bodies of evidence. We did not present pooled estimates for meta-analyses of less than six studies except in the case of a small number of highly clinically

and statistically homogeneous trials (e.g., NRT among pregnant women). We also narratively described results rather than presenting pooled estimates in cases of substantial or considerable statistical heterogeneity produced in meta-analyses. In the absence of review-generated forest plots, we created these plots to illustrate individual study-level results. Nineteen of the 22 primary reviews were Cochrane reviews. The general consistency and rigor of methods employed by authors of these reviews[97] strengthen this review of reviews. We quality rated each review according to AMSTAR criteria and relied upon the available best quality reviews for each body of evidence.

We did not describe or cite individual trials because of the large volume of trials represented across the primary reviews (over 800). While we did cite individual trials for descriptive and clarifying purposes, our intent was not to call them out as exemplar interventions or studies. Although our text and descriptive tables provide some information on the types of interventions included in the bodies of evidence, we did not include a detailed description of each intervention or replicate the study characteristics data that were presented by the original review authors. More detailed information is available in the original reviews.

Because the included reviews were not mutually exclusive in their eligibility criteria and, as a result, were not mutually exclusive in their included studies, there are individual trials that are represented in more than one review and/or meta-analysis, particularly for trials related to behavioral interventions in adults. We could not address this overlap by recalculating all of the estimates reported in reviews, but we do not expect such adjustments would alter our conclusions. By basing our estimates on primary reviews rather than reporting results from multiple reviews, we likely mitigated this potential shortcoming.

We focused our review on systematic reviews that included health, cessation, or adverse event outcomes as primary outcomes. We included studies that were applicable to primary care. We did not include reviews or abstract data for other interventions, such as harm reduction, relapse prevention, or non-first-line FDA approved medications. Recent reviews on these subjects do exist, however, and some readers may find these of interest.[211-219]

Within the individual reviews, there were some limitations in the statistical analyses that are worth noting. In several of the main meta-analyses, for example, authors treated comparisons between different trial arms as separate studies in the analyses and were not consistent in their reporting or handling of multiple comparisons from a single trial in meta-analysis. For instance, a study with two active intervention arms (e.g., group 1 low-intensity and group 2 high-intensity) and one control group (group 3) was often included twice in one meta-analysis (group 1 versus group 3 and group 2 versus group 3). In essence, the control group was represented twice within the analysis, which inflated the total number of control participants and violated the assumption of independent observations. Unless correctly accounted for, this can result in slight overestimation of the precision of the pooled estimate confidence (e.g., a narrower confidence interval). To account for this, we interpreted confidence intervals close to null in these cases cautiously.

In addition, the default Mantel-Haenszel fixed-effect methods of meta-analysis used for most of the primary reviews assumes that the true effect of the intervention (in both magnitude and

direction) is the same value in every study (i.e., fixed). The fixed effect model is appropriate if there is reason to believe that all studies are functionally similar (e.g., five studies conducted by the same researchers using the same protocol) and the goal is to compute the common effect that will be generalized to other examples of this same population. Fixed effect models are also used when event rates are low (e.g., ranging from 1% to 5%). In all of our included reviews, however, the participants and interventions differed in ways that could impact the results, and, as a result, one cannot really assume a common effect size. In these cases, random effects models are generally preferable to fixed effects models. Readers should note this limitation when interpreting the results of the pooled analyses.

The two primary reviews related to the effectiveness of NRT and bupropion SR declared potential conflicts of interest of the review authors including being involved in some of the included trials and receiving funds for consultancy work on behalf of the drug sponsors. In addition, review authors identified evidence of possible publication bias in some of the reviews. The review on the effectiveness of NRT among adults by Stead (2012a) and the review on combined pharmacotherapy and behavioral interventions also by Stead (2012b), for example, likely both include publication bias due to unpublished trials of NRT. In both, a funnel plot suggested some evidence of asymmetry with a few small to moderately sized trials finding effects in an unfavorable direction. As the authors of these reviews conclude, however, it is unlikely that the pooled estimates would change substantially if additional smaller studies with lower estimates were included given the large number of trials in these analyses. If this were true, however, the magnitude of effects may be smaller than the estimates we reported from the reviews.

While we did not reevaluate the risk of bias within individual trials, several limitations are applicable to all included studies. Biochemical validation of self-reported quitting ranged from 17 percent to 100 percent of trials within the included reviews. Most of the reviews that had a smaller percentage of included studies that required biochemical validation included a higher percentage of large community-based samples and included limited face-to-face contact (e.g., print-based self-help materials, telephone counseling, and computer-based interventions). It should be noted that the Society for Research on Nicotine and Tobacco subcommittee on measurement considers that verification is not necessary under these conditions.[220] It is also important to remember that while the validation of quitting will almost always reduce the absolute quit rate, the absence of validation will only lead to an overestimate of effects if intervention participants are more likely to misreport abstinence than control group participants. The likelihood of differential misreporting is small among those studies of large community-based samples with limited face-to-face contact.

Finally, the mechanism by which adverse events are recorded (generally passively) makes them susceptible to underreporting. As a result, these findings may be less reliable than for those of efficacy.

Applicability

Most of the included studies within each review were conducted in North America and, as such,

should be applicable to the US health system. Most studies enrolled individuals who were all current smokers (or in some cases tobacco users or recent quitters) with varying degrees of baseline smoking (i.e., cigarettes smoked per day) and nicotine dependence. These trials took place within a very wide range of settings using different types of providers and included individuals with smoking-related disease and those with mental health conditions. The literature almost exclusively addressed treatment for cigarette smoking, as opposed to the use of other forms of tobacco, so the results may not be generalizable to all forms of tobacco. The homogeneity of results across interventions and specific populations reflects the general applicability of the evidence. To that end, we believe the body of evidence represented in this review-of-review is very applicable to primary care providers in the US.

Comparison With 2008 Public Health Service Guideline and Other Related Reviews

The findings of our review of reviews are generally consistent with the 2008 US Public Health Service (PHS) Guideline (stated as Guideline hereafter) that serve as the basis for the current 2009 USPSTF recommendation.[3,221] We similarly found consistent evidence of effectiveness among general adults for physician advice to quit; varying formats of behavioral interventions (telephone counseling, individual and group counseling); and all three first-line FDA-approved medications as well as for behavioral interventions among pregnant women. There are, however, a few areas within the Guideline that were not fully addressed in our review of reviews or that were not entirely consistent with our findings.

In addition to strongly recommending use of all first-line FDA-approved medications (NRT, bupropion SR, and varenicline) for cessation, the Guideline also recommended certain combinations of medications including (1) long-term (> 14 weeks) nicotine patch + other NRT (gum or spray); (2) the nicotine patch + the nicotine inhaler; and (3) the nicotine patch and bupropion SR. The included Stead (2012a) review[140] found that trials that compared the use of two types of NRT with the use of a single type showed a statistically significantly greater cessation effect. There were only two trials included that reported the direct effect of NRT + bupropion SR versus placebo. One of these trials found a nearly four-fold greater quit rate among those receiving NRT patch and bupropion SR. The other study evaluated NRT *lozenge* + bupropion SR and found no difference with a placebo group.[140]

The Guideline concluded a "strong" dose-response relationship between the session length of person-to-person contact and successful treatment outcomes and stated that intensive interventions were more effective than less intensive interventions and should be used whenever possible. Based on their 2000 analysis, the estimated effects (odds ratio [OR]) of trials with 4-30 minutes contact time was 1.9 (95% CI, 1.1 to 1.8); the estimated effects for trials with 31-90 minutes was 3.0 (95% CI, 2.3 to 3.8); and the estimated effects for trials with 91-300 minutes of contact time, compared with minimal controls, was 3.2 (95% CI, 2.3 to 4.6) (PHS Guideline Table 6.9). Similarly, the Guideline concluded that there was a strong relationship between the number of counseling sessions, when combined with medication, and the likelihood of quitting (PHS Guideline Table 6.23). The reviews included in our review of reviews also suggested higher effect sizes among interventions of greater intensity. However, there was no clear

evidence to support intervention modification by total number of sessions or duration of personal contact.[136,138,139,142] While direct comparisons within trials between intensive versus minimal physician advice suggested an advantage of more intensive advice, this was small to nonexistent among smokers not selected as having smoking-related disease.[139]

A 2000 meta-analysis within the Guideline also concluded that behavioral smoking cessation interventions that are delivered in multiple formats increase abstinence rates and should be encouraged. For example, they found that treatment that used three or four format types (e.g., self-help materials, individual counseling, telephone support) were especially effective (OR 2.5 [95% CI, 2.1 to 3.0]) (PHS Guideline Table 6.14). We were not able to assess this effect within our included reviews.

All of the interventions that were found to be effective among the general adult population in the Guideline were also recommended for all individuals who smoke, including: those of low socioeconomic status; lesbian/gay/bisexual/transgender smokers; hospitalized smokers; HIV-positive smokers; smokers with medical comorbidities; older smokers; smokers with psychiatric disorders; including substance use disorders; racial and ethnic minorities; and women smokers. Specific groups such as pregnant women are typically excluded from cessation trials among the general adult population, thus, they were covered separately in the Guideline.

For pregnant women, the Guideline recommends that person-to-person psychosocial interventions that exceed minimal advice to quit be offered at the first prenatal visit as well as throughout the course of pregnancy. This recommendation was based on a 2008 meta-analysis that found a 80 percent higher odds of quitting smoking among those taking part in a psychosocial intervention versus usual care (PHS Guideline Table 7.5). The Guideline only included three RCTs of nicotine patch versus placebo among pregnant women—the same three were included in our review of reviews.[185,186,189] Based on these three trials, no recommendation was made regarding medication use during pregnancy.

We did not include a number of other topics that were meta-analyzed as part of the PHS Guideline, including: screening for tobacco use; providing tobacco treatment as a health care insurance benefit; nonfirst-line FDA-approved medications; or systems-level interventions. Readers interested in those subjects are encouraged to review data presented in the Guideline. Additionally, because of our approach, we were limited by the included reviews in the extent to which we could comment on the effectiveness of specific intervention characteristics (e.g., intensity of person-to-person clinical contact; type of clinician; types and formats of behavioral treatments; and specific populations).

Our review of reviews differs from another ‘overview of reviews’ conducted by Cahill and colleagues[222] on the effectiveness and safety of pharmacotherapies for tobacco cessation in that: we did not limit our inclusion to Cochrane reviews; we included behavioral interventions in addition to pharmacotherapies; we compared numerous reviews for consistency in results; and we included special attention to reviews among pregnant women and those with mental health conditions. Despite these differences, there was some overlap in the findings between our review and the Cahill overview of reviews on pharmacotherapy, with both finding that NRT, bupropion SR, and varenicline were all superior to placebo for smoking cessation and that none of them

appear to have a risk of adverse events that would negate their use among the general adult population. This result is probably not surprising given that the Cahill review used the same three Cochrane reviews that served as the basis for our primary results. It is important to note, however, that the version of the review on bupropion SR included in the Cahill review was last updated in 2009 as opposed to the version we used which was updated in 2013.[121] The Cahill overview review also reported the results of a network meta-analysis, finding increased odds of quitting for all three drugs versus placebo, but also suggesting varenicline may be superior to both NRT and bupropion SR.

In addition, a review of reviews and evidence-based recommendations for prevention of tobacco use and second-hand smoke exposure during pregnancy was recently published by the World Health Organization.[12] Their analysis of the effects of smoking cessation interventions primarily relied on earlier versions of the Coleman and Chamberlain reviews that were the basis of the findings in our report. As such, their estimated pooled effects, qualitative results, and synthesis correspond closely to ours – with evidence of benefits for behavioral interventions, but absent or thin evidence on the efficacy or harms of pharmacotherapy for smoking cessation during pregnancy. The World Health Organization report also outlined important research questions to pursue with regard to conducting research and testing interventions on smoking cessation during pregnancy, both for behavioral and pharmacological cessation aids.

Policy Implications of Tobacco Cessation Evidence

In 2010, the Affordable Care Act (ACA) required all new private health insurance plans to cover preventive services recommended by the USPSTF with an A or B recommendation, with no cost-sharing for the patient.[223] As such, the ACA requires that tobacco cessation pharmacotherapy and counseling services be covered at no cost to the patient. Specific sections of the law as they relate to tobacco cessation can be found here: http://www.ctri.wisc.edu/Insurers/HeathReformTobaccoSummary.pdf. When the ACA was passed, the Act required providers to cover tobacco cessation services, but provided little guidance on which services should be covered. This led to concerns that the lack of specificity related to the ACA tobacco cessation benefit would diminish the number of health insurance companies that provided the full range of mandated coverage.

A 2012 review by Georgetown University's Health Policy Institute found significant variation in the implementation of tobacco cessation treatment coverage across private health insurance contracts.[224] Only four of the 39 private health plans evaluated clearly covered a full range of evidence-based tobacco cessation services. Contract language contained vague or conflicting terminology that made it impossible to determine which–or even whether–tobacco cessation services were covered and whether there was cost-sharing for these services. None of the 39 reviewed contracts did all of the following: 1) stated clearly that tobacco cessation treatment was a covered benefit (without general exclusions); 2) provided coverage for individual, group, and phone counseling along with FDA-approved tobacco cessation medications; 3) provided tobacco cessation treatments by in-network providers with no cost-sharing; and 4) provided access to treatment without prerequisites, such as medical necessity or health risk assessment.

In response to these concerns, a number of nonprofit organizations prepared a joint letter to the U.S. Department of Health and Human Services (DHHS) asking for clear and comprehensive guidance on the tobacco cessation benefit in the ACA regulations.[225] On May 2, 2014, as part of a larger ACA Guidance Document, DHHS released details on what insurers must cover regarding tobacco cessation services.[226] Insurers are considered to be in compliance if the plan or issuer covers the following without cost-sharing: screening for tobacco use and, for those who use tobacco products, at least two tobacco cessation attempts per year. Covering a cessation attempt includes coverage for four tobacco cessation counseling sessions of at least 10 minutes each (including telephone counseling, group counseling and individual counseling) without prior authorization and all FDA-approved tobacco cessation medications (including both prescription and OTC medications) for a 90-day treatment regimen, when prescribed by a health care provider without prior authorization.

Future Research Needs

Our synthesis and source reviews identified a number of areas where more research is warranted. In terms of pharmacotherapy cessation interventions conducted among adults, direct comparisons between different combinations and classes of drugs would be informative (e.g., use of combinations of NRT and bupropion SR versus placebo; NRT versus varenicline, bupropion SR versus varenicline). The evidence base for trials of varenicline, although consistent, is relatively smaller than that of NRT and bupropion SR. Further varenicline trials would also be useful, particularly those that closely monitor harms along with evaluating effectiveness. In contrast, more research on NRT versus placebo is unlikely to change our understanding of the treatment. The incidence of serious adverse events related to all three drugs should be closely monitored and described with greater precision than is currently provided. This includes long-term monitoring of varenicline to clarify the possibility of its implication in neuropsychiatric and cardiovascular events.

It is unlikely that the main findings of our review of reviews would be altered by additional trials of combined pharmacotherapy and behavioral interventions, behavioral support as an adjunct to pharmacotherapy, behavioral advice and counseling by health care providers, and telephone counseling compared with ‘usual care’ or minimal intervention controls. Future research could contribute to further understanding about the effects of various intensities of treatment, particular settings for treatment, or a treatment’s effect among specific populations. This could include, for example, identifying the optimal amount of behavioral support to use with pharmacotherapy. Further research focusing on additional ways to personalize and tailor self-help materials and their effectiveness would also be beneficial. Additionally, more research is needed on different types of mobile phone- and internet-based cessation interventions, including text messaging and smartphone applications, which have very high potential applicability.

Among pregnant women, future research on the benefit and safety of NRT is warranted, including an assessment of optimal dosage and timing of treatment. Trials investigating the effects of bupropion SR and varenicline are required, if they are judged to be ethical and feasible. A recent pilot RCT on the safety and efficacy of bupropion SR for smoking cessation during pregnancy identified a number of challenges in the field and lessons to inform future trials.[227]

Screening of 820 women yielded only 11 women eligible and willing to consent, prompting the authors to recommend large multisite studies of pharmacotherapy. Careful collection of adverse events and systems for deriving long-term consequences of exposure during pregnancy is important in future trials as well. Despite the established importance of NRT for aiding cessation in general populations, it is surprising how few studies of NRT use have been conducted during pregnancy since exposure to nicotine is present with smoking or with NRT. Recent evidence of child health benefits from 2 year followup on the largest NRT trial highlight the importance of further research. For behavioral and NRT interventions, effort to identify and enroll more representative samples of women into trials is needed to ensure intervention effects are observed in less select populations, or to simply report clearly on the characteristics of women approached who declined participation. The effects of smoking cessation interventions on perinatal health outcomes are not recorded uniformly, and future behavioral trials should collect a comprehensive set of key outcomes, similar to those provided in recent NRT trials. Well-powered trials of behavioral therapies that show promise for strong effects could serve to make important contributions to maternal and child health. Although few have been conducted, trials using incentives to aid smoking cessation efforts suggest possibly strong effects, although it is unknown how long-term cessation efforts are affected by this kind of short-term motivation. Different interventions across pregnancy, postpartum, and beyond may also be beneficial and should include longer-term trials that combine multiple interventions in sequence and their consequences for fetal, infant, child and maternal health would be informative.

Evidence on the effectiveness of smoking cessation interventions among individuals with mental health conditions is restricted to only a few small studies. Given the high prevalence of smoking among those with mental illness, continued research on the effects of cessation interventions on health, cessation, and harms outcomes is justified.

As always, replicating promising interventions is a very important method that will strengthen the evidence base and should be supported.

Conclusion

The extensive evidence on strategies to help people stop smoking reviewed in this report confirms the effectiveness of a range of pharmacological and behavioral interventions, alone and in combination, for smoking cessation in adults. Behavioral interventions are especially applicable to pregnant women and patients with some types of mental health condition. We also identified areas where evidence is thin, but suggestive, and where the current evidence could be bolstered or extended, particularly for adults with serious mental illness and pregnant women. Clinicians have an array of tools to choose from to aid the smoking cessation efforts of their patients, and can directly offer, refer, or prescribe those that their patients find most acceptable, with informed consideration of the likely magnitude of benefits for 6-month cessation and beyond from different behavioral and pharmacological interventions, and their combination.

References

1. U.S.Preventive Services Task Force. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2009 Apr 21;150(8):551-5. PMID: 19380855.
2. Fiore MC. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA 2000 Jun 28;283(24):3244-54. PMID: 10866874.
3. Fiore, MC, jaen, CR, Baker, TB. Treating Tobacco Use and Dependence: 2008 Update (Clinical Practice Guideline). U.S. Department of Health and Human Services; 2008. PMID: None.
4. Cobb NK, Byron MJ, Abrams DB, et al. Novel nicotine delivery systems and public health: the rise of the "e-cigarette". Am J Public Health 2010 Dec;100(12):2340-2. PMID: 21068414.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Washington D.C.: American Psychiatric Association; 1994. PMID: None.
6. World Health Organization. International statistical classification of diseases and related health problems. Washington D.C.: World Health Organization; 1992. PMID: None.
7. Baker TB, Breslau N, Covey L, et al. DSM criteria for tobacco use disorder and tobacco withdrawal: a critique and proposed revisions for DSM-5. Addiction 2012 Feb;107(2):263-75. PMID: 21919989.
8. Office on Smoking and Health. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2010. PMID:.
9. Hatsukami DK, Stead LF, Gupta PC. Tobacco addiction. Lancet 2008 Jun 14;371(9629):2027-38. PMID:.
10. U.S.Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department 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; 2014. PMID: None.
11. Office on Smoking and Health. Women and Smoking: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2001. PMID:.
12. World Health Organization. WHO Recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy. Geneva, Switzerland: World Health Organization; 2013. PMID: None.
13. Jamal A, Agaku IT, O'Connor E, et al. Current cigarette smoking among adults--United States, 2005-2013. MMWR Morb Mortal Wkly Rep 2014 Nov 28;63(47):1108-12. PMID: 25426653.
14. Cook BL, Wayne GF, Kafali EN, et al. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. JAMA 2014 Jan 8;311(2):172-82. PMID: 24399556.

15. Centers for Diesease Control and Prevention. Vital Signs: Current Cigarette Smoking Among Adults Aged >=18 Years with Mental Illness - United States, 2009-2011. 62(05). Morbidity and Mortality Weekly Report; 2013. PMID: None.
16. McClave AK, McKnight-Eily LR, Davis SP, et al. Smoking characteristics of adults with selected lifetime mental illnesses: results from the 2007 National Health Interview Survey. Am J Public Health 2010 Dec;100(12):2464-72. PMID:.
17. Substance Abuse and Mental Health Services Administration. The NSDUH Report: Smoking and Mental Illness. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013. PMID: None.
18. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013. PMID: None.
19. Centers for Disease Control and Prevention. Quitting smoking among adults--United States, 2001-2010. MMWR Morb Mortal Wkly Rep 2011 Nov 11;60(44):1513-9. PMID: 22071589.
20. U.S.Department of Health and Human Services. The Health Benefits of Smoking Cessation. A Report of the Surgeon General. YO-K-116. Centers for Disease Control; 1990. PMID: None.
21. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013 Jan 24;368(4):341-50. PMID: 23343063.
22. Gellert C, Schottker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. Arch Intern Med 2012 Jun 11;172(11):837-44. PMID: 22688992.
23. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med 2005 Feb 15;142(4):233-9. PMID: 15710956.
24. Rose G, Hamilton PJ. A randomised controlled trial of the effect on middle-aged men of advice to stop smoking. J Epidemiol Community Health 1978 Dec;32(4):275-81. PMID: 370171.
25. Rose G, Colwell L. Randomised controlled trial of anti-smoking advice: final (20 year) results. J Epidemiol Community Health 1992 Feb;46(1):75-7. PMID: 1573365.
26. Kawachi I, Colditz GA, Stampfer MJ, et al. Smoking cessation and decreased risk of stroke in women. JAMA 1993 Jan 13;269(2):232-6. PMID: 8417241.
27. Wannamethee SG, Shaper AG, Whincup PH, et al. Smoking cessation and the risk of stroke in middle-aged men. JAMA 1995 Jul 12;274(2):155-60. PMID: 7596004.
28. Taylor G, McNeill A, Girling A, et al. Change in mental health after smoking cessation: systematic review and meta-analysis. BMJ 2014;348:g1151. PMID:.
29. U.S.Food and Drug Administration. Smoking Cessation Products to Help You Quit. U.S.Department of Health and Human Services; 2012. http://www.fda.gov/tobaccoproducts/resourcesforyou/ucm168231.htm. Accessed October 15, 2014. PMID: None.
30. Food and Drug Administration. Modifications to labeling of nicotine replacement therapy products for over-the-counter human use. Federal Register 2013 Apr 2;78(63):19718-21. PMID: None.

31. Herman AI, Sofuoglu M. Comparison of available treatments for tobacco addiction. Curr Psychiatry Rep 2010 Oct;12(5):433-40. PMID:.
32. Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control 2014 Jul;23 Suppl 3:iii3-iii9. PMID: 24935895.
33. Etter JF, Bullen C, Flouris AD, et al. Electronic nicotine delivery systems: a research agenda. Tob Control 2011 May;20(3):243-8. PMID:.
34. Goniewicz ML, Kuma T, Gawron M, et al. Nicotine levels in electronic cigarettes. Nicotine Tob Res 2013 Jan;15(1):158-66. PMID: 22529223.
35. Cameron JM, Howell DN, White JR, et al. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. Tob Control 2014 Jan;23(1):77-8. PMID: 23407110.
36. Trehy ML, Ye W, Hadwiger ME, et al. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. Journal of Liquid Chromatography and Related Technologies 2011;34(14):1442-58. PMID: None.
37. Davis B, Dang M, Kim J, et al. Nicotine concentrations in electronic cigarette refill and do-it-yourself fluids. Nicotine Tob Res 2014 May 26 PMID: 24862971.
38. Food and Drug Administration. Electronic Cigarettes. Silver Spring, MD: U.S. Food and Drug Administration; 2014. PMID: None.
39. Food and Drug Administration. Proposed Rule: Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act. 2014. PMID: None.
40. Campaign for Tobacco-Free Kids. New study finds dramatic rise in youth exposure to e-cigarette ads on TV, underscores need for FDA to regulate e-cigarette marketing. 2014.
41. King BA, Patel R, Nguyen KH, et al. Trends in Awareness and Use of Electronic Cigarettes Among U.S. Adults, 2010-2013. Nicotine Tob Res 2014 Sep 19 PMID:.
42. Regan AK, Promoff G, Dube SR, et al. Electronic nicotine delivery systems: adult use and awareness of the 'e-cigarette' in the USA. Tob Control 2013 Jan;22(1):19-23. PMID: 22034071.
43. Adkison SE, O'Connor RJ, Bansal-Travers M, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. Am J Prev Med 2013 Mar;44(3):207-15. PMID: 23415116.
44. Cummins S, Zhu S, Tedeschi G, et al. Use of e-cigarettes by individuals with mental health conditions. Tob Control 2014 May 12 PMID:.
45. World Health Organization. Marketers of electronic cigarettes should halt unproved therapy claims. 2008. PMID: None.
46. Auf R. Electronic cigarettes and smoking cessation: a quandary? Lancet 2014 Feb 1;383(9915):408. PMID: 24485577.
47. Benowitz NL. Emerging nicotine delivery products. Implications for public health. Ann Am Thorac Soc 2014 Feb;11(2):231-5. PMID: 24575992.
48. Bialous SA, Sarma L. Electronic cigarettes and smoking cessation: a quandary? Lancet 2014 Feb 1;383(9915):407-8. PMID: 24485576.
49. Brody JS. The promise and problems of e-cigarettes. Am J Respir Crit Care Med 2014 Feb 15;189(4):379-80. PMID: 24528311.
50. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes and smoking cessation: a quandary? - Authors' reply. Lancet 2014 Feb 1;383(9915):408-9. PMID: 24485579.

51. Bullen C, Knight-West O, O'Brien B, et al. Evidence, not conjecture, should guide clinical practice and policies on e-cigarettes. BMJ 2014;348:g2008. PMID: 24614753.
52. Chapman S. E-cigarettes: does the new emperor of tobacco harm reduction have any clothes? Eur J Public Health 2014 Apr 26. PMID: 24769546.
53. Doyle C, Patterson S, Scott J. Electronic cigarettes and smoking cessation: a quandary? Lancet 2014 Feb 1;383(9915):408. PMID: 24485578.
54. Glynn TJ. E-cigarettes and the future of tobacco control. CA Cancer J Clin 2014 Mar 14 PMID: 24633865.
55. Hitchman SC, McNeill A, Brose LS. Electronic cigarettes: time for an accurate and evidence-based debate. Addiction 2014 Jun;109(6):867-8. PMID: 24796396.
56. Cobb NK, Abrams DB. The FDA, e-cigarettes, and the demise of combusted tobacco. N Engl J Med 2014 Oct 16;371(16):1469-71. PMID:.
57. Maziak W. Potential and pitfalls of e-cigarettes. JAMA 2014 May 14;311(18):1922. PMID: 1869202.
58. Abrams DB. Potential and pitfalls of e-cigarettes--reply. JAMA 2014 May 14;311(18):1922-3. PMID: 1869204.
59. Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic Cigarettes: A Policy Statement From the American Heart Association. Circulation 2014 Aug 24 PMID: 25156991.
60. Fiore MC, Schroeder SA, Baker TB. Smoke, the chief killer - Strategies for targeting combustible tobacco use. New England Journal of Medicine 2014;370(4):297-9. PMID: 24450888.
61. Wagener TL, Siegel M, Borrelli B. Electronic cigarettes: achieving a balanced perspective. Addiction 2012 Sep;107(9):1545-8. PMID: 22471757.
62. Caponnetto P, Russo C, Bruno CM, et al. Electronic cigarette: a possible substitute for cigarette dependence. Monaldi Arch Chest Dis 2013 Mar;79(1):12-9. PMID: 23741941.
63. Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? JAMA 2014 Jan 8;311(2):135-6. PMID: 24399548.
64. Callahan-Lyon P. Electronic cigarettes: human health effects. Tob Control 2014 May;23 Suppl 2:ii36-ii40. PMID: 24732161.
65. Chen IL, Husten CG. Introduction to tobacco control supplement. Tob Control 2014 May;23 Suppl 2:ii1-ii3. PMID: 24732156.
66. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control 2014 Mar;23(2):133-9. PMID: 23467656.
67. Hung DY, Leidig R, Shelley DR. What's in a setting?: Influence of organizational culture on provider adherence to clinical guidelines for treating tobacco use. Health Care Manage Rev 2013 Apr 30 PMID: 23636103.
68. Jamal A, Dube SR, Malarcher AM, et al. Tobacco use screening and counseling during physician office visits among adults--National Ambulatory Medical Care Survey and National Health Interview Survey, United States, 2005-2009. MMWR Morb Mortal Wkly Rep 2012 Jun 15;61 Suppl:38-45. PMID: 22695462.
69. Messer K, Trinidad DR, Al-Delaimy WK, et al. Smoking cessation rates in the United States: a comparison of young adult and older smokers. Am J Public Health 2008 Feb;98(2):317-22. PMID: 18172143.
70. Conroy MB, Majchrzak NE, Silverman CB, et al. Measuring provider adherence to tobacco treatment guidelines: a comparison of electronic medical record review, patient survey, and provider survey. Nicotine Tob Res 2005 Apr;7 Suppl 1:S35-S43. PMID: 16036268.

71. Chase EC, McMenamin SB, Halpin HA. Medicaid provider delivery of the 5A's for smoking cessation counseling. Nicotine Tob Res 2007 Nov;9(11):1095-101. PMID: 17978983.
72. Papadakis S, McDonald P, Mullen KA, et al. Strategies to increase the delivery of smoking cessation treatments in primary care settings: a systematic review and meta-analysis. Preventive Medicine 2010;51(3-4):199-213. PMID: 20600264.
73. Herie M, Connolly H, Voci S, et al. Changing practitioner behavior and building capacity in tobacco cessation treatment: the TEACH project. Patient Educ Couns 2012 Jan;86(1):49-56. PMID: 21612884.
74. Sheffer CE, Anders M, Brackman SL, et al. Tobacco intervention practices of primary care physicians treating lower socioeconomic status patients. Am J Med Sci 2012 May;343(5):388-96. PMID: 22008779.
75. Haug S, Meyer C, Ulbricht S, et al. Predictors and moderators of outcome in different brief interventions for smoking cessation in general medical practice. Patient Educ Couns 2010 Jan;78(1):57-64. PMID: 19660890.
76. Kandra KL, Ranney LM, Lee JG, et al. Physicians' attitudes and use of e-cigarettes as cessation devices, North Carolina, 2013. PLoS ONE 2014;9(7):e103462. PMID: 25072466.
77. England L, Anderson B, Tong V, et al. Screening practices and attitudes of obstetricians-gynecologists toward new and emerging tobacco products. Am J Obstet Gynecol 2014 May 29 PMID: 24881828.
78. Guide to Community Preventive Services. Reducing tobacco use and secondhand smoke exposure. 2013. PMID: None.
79. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info Libr J 2009 Jun;26(2):91-108. PMID: 19490148.
80. Becker L, Oxman A. Higgins J, Green S, editors. Cochrane Handbook for Systmatic Reviews of Interventions (Version 5.1.0). The Cochrane Collaboration; 2011. PMID: None.
81. Whitlock EP, Lin JS, Chou R, et al. Using existing systematic reviews in complex systematic reviews. Ann Intern Med 2008 May 20;148(10):776-82. PMID: 18490690.
82. U.S.Preventive Services Task Force. Procedure Manual. Rockville, MD: Agency for Healthcare Quality and Research; 2011. PMID: None.
83. Canadian Agency for Drugs and Technologies in Health. Electronic cigarettes: a review of the clinical evidence and safety. 2012. PMID: None.
84. Drummond MB, Upson D. Electronic cigarettes. Potential harms and benefits. Ann Am Thorac Soc 2014 Feb;11(2):236-42. PMID: 24575993.
85. Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther Adv Drug Saf 2014 Apr;5(2):67-86. PMID: 25083263.
86. Franck C, Budlovsky T, Windle SB, et al. Electronic cigarettes in north america: history, use, and implications for smoking cessation. Circulation 2014 May 13;129(19):1945-52. PMID: 24821825.
87. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation 2014 May 13;129(19):1972-86. PMID: 24821826.
88. Hajek P, Etter JF, Benowitz N, et al. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. Addiction 2014 Jul 31 PMID: 25078252.

89. Harrell PT, Simmons VN, Correa JB, et al. Electronic Nicotine Delivery Systems ("E-cigarettes"): Review of Safety and Smoking Cessation Efficacy. Otolaryngol Head Neck Surg 2014 Jun 4 PMID: 24898072.
90. Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. Tob Control 2013 Nov 20 PMID: 24259045.
91. Peralta AR, Guntur VP. Safety and efficacy of electronic cigarettes: a review. Mo Med 2014 May;111(3):238-44. PMID: 25011347.
92. Coleman T, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2012 PMID: 22972148.
93. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10. PMID: 17302989.
94. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009 Oct;62(10):1013-20. PMID: 19230606.
95. Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. PLoS ONE 2013;8(7):e69930. PMID: 23922860.
96. Cornell JE, Mulrow CD, Localio R, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. Ann Intern Med 2014 Feb 18;160(4):267-70. PMID: 24727843.
97. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. 2011. PMID:.
98. West R, Hajek P, Stead L, et al. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 2005 Mar;100(3):299-303. PMID: 15733243.
99. Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? Addiction 2010 Jul;105(7):1176-89. PMID: 20491721.
100. Barnes J, Dong CY, McRobbie H, et al. Hypnotherapy for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2010;Issue 10 PMID: 20927723.
101. Berlin I, Grange G, Jacob N, et al. Nicotine patches in pregnant smokers: randomised, placebo controlled, multicentre trial of efficacy. BMJ 2014;348:g1622. PMID: 24627552.
102. Bize R, Burnand B, Mueller Y, et al. Biomedical risk assessment as an aid for smoking cessation. Cochrane Database of Systematic Reviews 2012 PMID: 23235615.
103. Bodner ME, Dean E. Advice as a smoking cessation strategy: a systematic review and implications for physical therapists. Physiother Theory Pract 2009 Jul;25(5-6):369-407. PMID: 19842864.
104. Brown J. A review of the evidence on technology-based interventions for the treatment of tobacco dependence in college health. Worldviews Evid Based Nurs 2013 Aug;10(3):150-62. PMID: 23421669.
105. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013 Sep 9 PMID: 24029165.
106. Cahill K, Lancaster T, Green N. Stage-based interventions for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2010;Issue 11 PMID: 21069681.

107. Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. PLoS ONE 2013;8(6):e66317. PMID: 23826093.
108. Carr AB, Ebbert J. Interventions for tobacco cessation in the dental setting. Cochrane Database of Systematic Reviews: Reviews 2012;Issue 6 PMID: 22696348.
109. Carson K, V, Brinn MP, Peters M, et al. Interventions for smoking cessation in Indigenous populations. Cochrane Database of Systematic Reviews: Reviews 2012;Issue 1 PMID: 22258998.
110. Chamberlain C, O'Mara-Eves A, Oliver S, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev 2013;10:CD001055. PMID: 24154953.
111. Chen YF, Madan J, Welton N, et al. Effectiveness and cost-effectiveness of computer and other electronic aids for smoking cessation: a systematic review and network meta-analysis. Health Technol Assess 2012;16(38):1-v. PMID: 23046909.
112. Cheng HM, Chung YC, Chen HH, et al. Systematic review and meta-analysis of the effects of acupoint stimulation on smoking cessation. American Journal of Chinese Medicine 2012;40(3):429-42. PMID: 22745061.
113. Civljak M, Stead LF, Hartmann-Boyce J, et al. Internet-based interventions for smoking cessation. Cochrane Database Syst Rev 2013;7:CD007078. PMID: 23839868.
114. Di YM, May BH, Zhang AL, et al. A meta-analysis of ear-acupuncture, ear-acupressure and auriculotherapy for cigarette smoking cessation. Drug Alcohol Depend 2014 Jul 11 PMID: 25064021.
115. Ebbert J, Montori VM, Erwin PJ, et al. Interventions for smokeless tobacco use cessation. Cochrane Database of Systematic Reviews: Reviews 2011;Issue 2 PMID: 21328266.
116. Filion KB, Abenhaim HA, Mottillo S, et al. The effect of smoking cessation counselling in pregnant women: a meta-analysis of randomised controlled trials. BJOG An International Journal of Obstetrics and Gynaecology 2011;118(12):1422-8. PMID: 21880109.
117. Gierisch JM, Bastian LA, Calhoun PS, et al. Comparative Effectiveness of Smoking Cessation Treatments for Patients With Depression: A Systematic Review and Meta-analysis of the Evidence [Internet]. VA Evidence-based Synthesis Program Reports 2010 Nov. PMID:.
118. Hartmann-Boyce J, Lancaster T, Stead LF. Print-based self-help interventions for smoking cessation. Cochrane Database Syst Rev 2014;6:CD001118. PMID:.
119. Hettema JE, Hendricks PS. Motivational interviewing for smoking cessation: a meta-analytic review. J Consult Clin Psychol 2010 Dec;78(6):868-84. PMID: 21114344.
120. Huang Y, Li W, Yang L, et al. Long-term efficacy and safety of varenicline for smoking cessation: a systematic review and meta-analysis of randomized controlled trials. Journal of Public Health 2012;20(4):355-65. PMID: None.
121. Hughes JR, Stead LF, Hartmann BJ, et al. Antidepressants for smoking cessation. Cochrane Database of Systematic Reviews 2014 PMID: 24402784.
122. Hutton HE, Wilson LM, Apelberg BJ, et al. A systematic review of randomized controlled trials: Web-based interventions for smoking cessation among adolescents, college students, and adults. Nicotine Tob Res 2011 Apr;13(4):227-38. PMID: 21350042.
123. Johnston V, Westphal DW, Glover M, et al. Reducing smoking among indigenous populations: new evidence from a review of trials. Nicotine Tob Res 2013 Aug;15(8):1329-38. PMID: 23519776.

124. Lai Douglas TC, Cahill K, Qin Y, et al. Motivational interviewing for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2010;Issue 1 PMID: 20091612.
125. Likis FE, Andrews JC, Fonnesbeck CJ, et al. Smoking Cessation Interventions in Pregnancy and Postpartum Care. Evidence Report/Technology Assessment No. 214. Rockville, MD: Agency for Healthcare Research and Quality; 2014. PMID: None.
126. Liu JJ, Wabnitz C, Davidson E, et al. Smoking cessation interventions for ethnic minority groups: a systematic review of adapted interventions. Preventive Medicine 2013;57(6):765-75. PMID: 24076130.
127. Lumley J, Chamberlain C, Dowswell T, et al. Interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews: Reviews 2009;Issue 3. PMID: 19588322.
128. Mills EJ, Wu P, Lockhart I, et al. 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. PMID: 20626883.
129. Mills EJ, Wu P, Lockhart I, et al. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. Annals of Medicine 2012;44(6):588-97. PMID: 22860882.
130. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation 2014 Jan 7;129(1):28-41. PMID: 24323793.
131. Mottillo S, Filion KB, Belisle P, et al. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. European Heart Journal 2009;30(6):718-30. PMID: 19109354.
132. Myung SK, McDonnell DD, Kazinets G, et al. Effects of Web- and computer-based smoking cessation programs. Archives of Internal Medicine 2009;169(10):929-37. PMID: 19468084.
133. Myung SK, Ju W, Jung HS, et al. Efficacy and safety of pharmacotherapy for smoking cessation among pregnant smokers: a meta-analysis. BJOG 2012 Aug;119(9):1029-39. PMID: 22780818.
134. Nierkens V, Hartman MA, Nicolaou M, et al. Effectiveness of Cultural Adaptations of Interventions Aimed at Smoking Cessation, Diet, and/or Physical Activity in Ethnic Minorities. A Systematic Review. PLoS ONE 2013;8(10):e73373. PMID: 24116000.
135. 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. PMID: 22563098.
136. Rice VH, Stead LF. Nursing interventions for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2013;Issue 1 PMID: 23932719.
137. Shahab L, McEwen A. Online support for smoking cessation: a systematic review of the literature. Addiction 2009;104(11):1792-804. PMID: 19832783.
138. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2012;10:CD008286. PMID: 23076944.
139. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. Cochrane Database Syst Rev 2013;5:CD000165. PMID: 23728631.

140. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2012;Issue 1 PMID: 23152200.
141. Stead LF, Hartmann BJ, Perera R, et al. Telephone counselling for smoking cessation. Cochrane Database of Systematic Reviews 2013 PMID: 23934971.
142. Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2013;Issue 2 PMID: 23235680.
143. Su A, Buttenheim AM. Maintenance of Smoking Cessation in the Postpartum Period: Which Interventions Work Best in the Long-Term? Matern Child Health J 2013 Jun 29 PMID: 23812798.
144. Tahiri M, Mottillo S, Joseph L, et al. Alternative smoking cessation aids: a meta-analysis of randomized controlled trials. American Journal of Medicine 2012;125(6):576-84. PMID: 22502956.
145. Tran, K, Asakawa, K, Cimon, K, et al. Pharmacologic-based strategies for smoking cessation. 2010. PMID: None.
146. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database Syst Rev 2013;2:CD007253. PMID: 23450574.
147. Tzelepis F, Paul CL, Walsh RA, et al. Proactive telephone counseling for smoking cessation: meta-analyses by recruitment channel and methodological quality. J Natl Cancer Inst 2011 Jun 22;103(12):922-41. PMID: 21666098.
148. Ussher MH, Taylor AH, Faulkner GE. Exercise interventions for smoking cessation. Cochrane Database Syst Rev 2014;8:CD002295. PMID: 25170798.
149. van der Meer RM, Willemsen MC, Smit F, et al. Smoking cessation interventions for smokers with current or past depression. Cochrane Database Syst Rev 2013;8:CD006102. PMID: 23963776.
150. Villanti AC, McKay HS, Abrams DB, et al. Smoking-cessation interventions for U.S. young adults: a systematic review. Am J Prev Med 2010 Dec;39(6):564-74. PMID: 21084078.
151. White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev 2014;1:CD000009. PMID:.
152. Whittaker R, McRobbie H, Bullen C, et al. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev 2012;11:CD006611. PMID: 23152238.
153. Zbikowski SM, Magnusson B, Pockey JR, et al. A review of smoking cessation interventions for smokers aged 50 and older. Maturitas 2012 Feb;71(2):131-41. PMID: 22209349.
154. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2012;Issue 4 PMID: 22513936.
155. Croghan GA, Sloan JA, Croghan IT, et al. Comparison of nicotine patch alone versus nicotine nasal spray alone versus a combination for treating smokers: a minimal intervention, randomized multicenter trial in a nonspecialized setting. Nicotine Tob Res 2003 Apr;5(2):181-7. PMID: 12745490.
156. Lerman C, Kaufmann V, Rukstalis M, et al. Individualizing nicotine replacement therapy for the treatment of tobacco dependence: a randomized trial. Ann Intern Med 2004 Mar 16;140(6):426-33. PMID: 15023708.

157. Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch Gen Psychiatry 2009 Nov;66(11):1253-62. PMID: 19884613.
158. Schnoll RA, Martinez E, Tatum KL, et al. Nicotine patch vs. nicotine lozenge for smoking cessation: an effectiveness trial coordinated by the Community Clinical Oncology Program. Drug Alcohol Depend 2010 Mar 1;107(2-3):237-43. PMID: 20004065.
159. Smith SS, McCarthy DE, Japuntich SJ, et al. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. Arch Intern Med 2009 Dec 14;169(22):2148-55. PMID: 20008701.
160. Tonnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. Eur Respir J 2000 Oct;16(4):717-22. PMID: 11106218.
161. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999 Mar 4;340(9):685-91. PMID: 10053177.
162. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997 Oct 23;337(17):1195-202. PMID: 9337378.
163. Swan GE, McAfee T, Curry SJ, et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: a randomized trial. Arch Intern Med 2003 Oct 27;163(19):2337-44. PMID: 14581254.
164. Hall SM, Humfleet GL, Reus VI, et al. Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psychiatry 2002 Oct;59(10):930-6. PMID: 12365880.
165. McCarthy DE, Piasecki TM, Lawrence DL, et al. A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. Nicotine Tob Res 2008 Apr;10(4):717-29. PMID: 18418793.
166. Schmitz JM, Stotts AL, Mooney ME, et al. Bupropion and cognitive-behavioral therapy for smoking cessation in women. Nicotine Tob Res 2007 Jun;9(6):699-709. PMID: 17558827.
167. Piper ME, Federman EB, McCarthy DE, et al. Efficacy of bupropion alone and in combination with nicotine gum. Nicotine Tob Res 2007 Sep;9(9):947-54. PMID: 17763111.
168. Aubin HJ, Bobak A, Britton JR, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 2008 Aug;63(8):717-24. PMID: 18263663.
169. 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 Apr;74(4):771-8. PMID: 20154405.
170. Cinciripini PM, Robinson JD, Karam-Hage M, et al. Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. JAMA Psychiatry 2013 May;70(5):522-33. PMID: 23536105.
171. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006 Jul 5;296(1):47-55. PMID: 16820546.

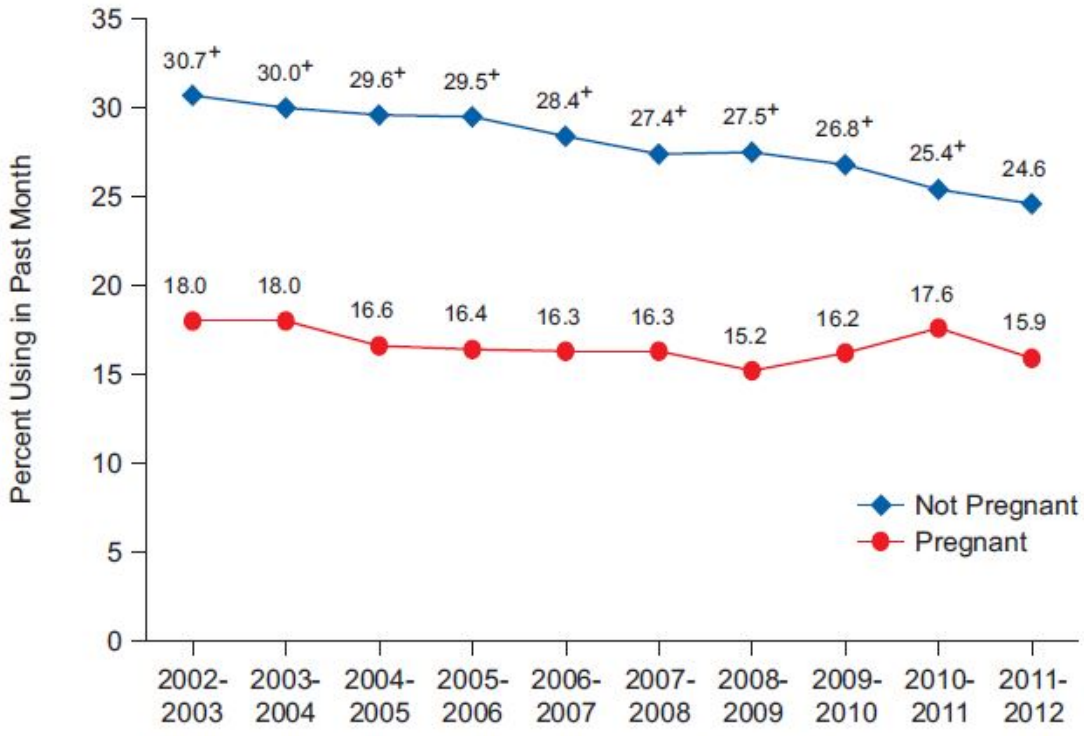
172. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006 Jul 5;296(1):56-63. PMID: 16820547.
173. Nides M, Oncken C, Gonzales D, et al. 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 Aug 14;166(15):1561-8. PMID: 16908788.
174. White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2011;Issue 1 PMID: 21249644.
175. Rodgers A, Corbett T, Bramley D, et al. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. Tob Control 2005 Aug;14(4):255-61. PMID: 16046689.
176. Free C, Whittaker R, Knight R, et al. Txt2stop: a pilot randomised controlled trial of mobile phone-based smoking cessation support. Tob Control 2009 Apr;18(2):88-91. PMID: 19318534.
177. Free C, Knight R, Robertson S, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet 2011 Jul 2;378(9785):49-55. PMID: 21722952.
178. Borland R, Balmford J, Benda P. Population-level effects of automated smoking cessation help programs: a randomized controlled trial. Addiction 2013 Mar;108(3):618-28. PMID: 22994457.
179. Whittaker R, Dorey E, Bramley D, et al. A theory-based video messaging mobile phone intervention for smoking cessation: randomized controlled trial. J Med Internet Res 2011;13(1):e10. PMID: 21371991.
180. Swan GE, McClure JB, Jack LM, et al. Behavioral counseling and varenicline treatment for smoking cessation. Am J Prev Med 2010 May;38(5):482-90. PMID: 20409497.
181. Parkes G, Greenhalgh T, Griffin M, et al. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. BMJ 2008 Mar 15;336(7644):598-600. PMID: 18326503.
182. Bovet P, Perret F, Cornuz J, et al. Improved smoking cessation in smokers given ultrasound photographs of their own atherosclerotic plaques. Prev Med 2002 Feb;34(2):215-20. PMID: 11817917.
183. Johnson KM, Lando HA, Schmid LS, et al. The GAINS project: outcome of smoking cessation strategies in four urban Native American clinics. Giving American Indians No-smoking Strategies. Addict Behav 1997 Mar;22(2):207-18. PMID: 9113215.
184. Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. New England Journal of Medicine 2012 Mar 1;366(9):808-18. PMID: 22375972.
185. Wisborg K, Henriksen TB, Jespersen LB, et al. Nicotine patches for pregnant smokers: a randomized controlled study. Obstet Gynecol 2000 Dec;96(6):967-71. PMID: 11084187.
186. Kapur B, Hackman R, Selby P, et al. Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. Curr Ther Res Clin Exp 2001;62(4):274-8. PMID: None.

187. Hotham ED, Gilbert AL, Atkinson ER. A randomised-controlled pilot study using nicotine patches with pregnant women. Addict Behav 2006 Apr;31(4):641-8. PMID: 15985339.
188. Oncken C, Dornelas E, Greene J, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. Obstet Gynecol 2008 Oct;112(4):859-67. PMID: 18827129.
189. Pollak KI, Oncken CA, Lipkus IM, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. Am J Prev Med 2007 Oct;33(4):297-305. PMID: 17888856.
190. Cooper S, Taggar J, Lewis S, et al. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. The Lancet Respiratory Medicine 2014 Aug 10(9):728-37. PMID: 25127405.
191. Tsoi DT, Porwal M, Webster AC. Efficacy and safety of bupropion for smoking cessation and reduction in schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2010 May;196(5):346-53. PMID: 20435957.
192. Fucito LM, Bars MP, Forray A, et al. Addressing the evidence for FDA nicotine replacement therapy label changes: a policy statement of the Association for the Treatment of Tobacco use and Dependence and the Society for Research on Nicotine and Tobacco. Nicotine Tob Res 2014 Jul;16(7):909-14. PMID: 24919399.
193. Koegelenberg CF, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. JAMA 2014 Jul 9;312(2):155-61. PMID: 25005652.
194. Ramon JM, Morchon S, Baena A, et al. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. BMC Med 2014;12:172. PMID: 25296623.
195. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. JAMA 2014 Jan 8;311(2):155-63. PMID: 24399554.
196. Food and Drug Administration. CHANTIX (varenicline) Label: Efficacy supplement with clinical data to support. Silver Springs, MD: FDA Center for Drug Evaluation and Research; 2013.
197. Food and Drug Administration. ZYBAN (bupropion) Labeling Revision. Silver Springs, MD: FDA Center for Drug Evaluation and Research; 2014.
198. Food and Drug Administration. FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of cardiovascular adverse events. Silver Springs, MD: FDA Center for Drug Evaluation and Research; 2012.
199. Food and Drug Administration, Food and. FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events. Silver Springs, MD: FDA Center for Drug Evaluation and Research; 2011.
200. Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. Am J Psychiatry 2013 Dec 1;170(12):1460-7. PMID: 24030388.
201. ClinicalTrials.gov. Study To Evaluate Cardiac Assessments Following Different Treatments of Smoking Cessation Medications In Subjects With and Without Psychiatric Disorders (CATS). www.ClinicalTrials.gov; 2014. Accessed September 19, 2014.
202. Orr KK, Asal NJ. Efficacy of Electronic Cigarettes for Smoking Cessation. Ann Pharmacother 2014 Aug 18 PMID: 25136064.

203. Gualano MR, Passi S, Bert F, et al. Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies. J Public Health (Oxf) 2014 Aug 9 PMID: 25108741.
204. McRobbie H, Bullen C, Hartmann-Boyce J, et al. Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev 2014 Dec 17;12:CD010216. PMID:.
205. Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction 2011 Nov;106(11):2017-28. PMID: 21592253.
206. Cahn Z, Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? J Public Health Policy 2011 Feb;32(1):16-31. PMID: 21150942.
207. Orr MS. Electronic cigarettes in the USA: a summary of available toxicology data and suggestions for the future. Tob Control 2014 May;23 Suppl 2:ii18-ii22. PMID: 24732158.
208. Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. Tob Control 2014 May;23 Suppl 2:ii4-ii10. PMID: 24732162.
209. Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacol Ther 2009 May;122(2):125-39. PMID: 19268688.
210. Chatham-Stephens K, Law R, Taylor E, et al. Notes from the field: calls to poison centers for exposures to electronic cigarettes--United States, September 2010-February 2014. MMWR Morb Mortal Wkly Rep 2014 Apr 4;63(13):292-3. PMID: 24699766.
211. Hajek P, Stead LF, West R, et al. Relapse prevention interventions for smoking cessation. [Review][Update of Cochrane Database Syst Rev. 2009;(1):CD003999. PMID: 19160228.
212. National Institute for Health and Care Excellence. Tobacco harm reduction. London: National Institutes for Health and Care Excellence; 2013. PMID: None.
213. Lancaster T, Stead LF. Silver acetate for smoking cessation. Cochrane Database of Systematic Reviews 2012 PMID: 22972041.
214. Hajek P, Stead LF, West R, et al. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2009; Issue 1 PMID: 23963584.
215. Dhippayom T, Chaiyakunapruk N, Jongchansittho T. Safety of nortriptyline at equivalent therapeutic doses for smoking cessation: a systematic review and meta-analysis. Drug Safety 2011;34(3):199-210. PMID: 21332244.
216. Cahill K, Ussher MH. Cannabinoid type 1 receptor antagonists for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2011;Issue 3 PMID: 21412887.
217. Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2011;Issue 12 PMID: 22161436.
218. Stead LF, Hughes JR. Lobeline for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2012;Issue 2 PMID: 22336780.
219. Leaviss J, Sullivan W, Ren S, et al. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. Health Technol Assess 2014 May;18(33):1-120. PMID: 24831822.
220. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res 2002 May;4(2):149-59. PMID: 12028847.
221. Fiore MC. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report (Clinical Summary). Am J Prev Med 2008 Aug;35(2):158-76. PMID: 18617085.

222. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329. PMID: 23728690.
223. Quality, Affordable Health Care for Americans: Immediate Improvements in Health Care Coverage for All Americans, H.R. 3590, (December 24, 2009). PMID: None.
224. Kofman, M, Dunton, K, Senkewicz, M. Implementation of tobacco cessation coverage under the Affordable Care Act: Understanding how private health insurance policies cover tobacco cessation treatments. Washington D.C.: Healthy Policy Institute; 2012. PMID: None.
225. American Academy of Family Physicians e. Group Letter to Secretary Sebelius re: Comprehensive Cessation Benefit. 2014. PMID: None.
226. U.S.Department of Health and Human Services. FAQs about Affordable Care Act Implementation (Part XIX). 2014. PMID: None.
227. Stotts AL, Northrup TF, Cinciripini PM, et al. Randomized, Controlled Pilot Trial of Bupropion for Pregnant Smokers: Challenges and Future Directions. Am J Perinatol 2014 Aug 11 PMID: 25111040.
228. Combating Tobacco in Military and Veteran Populations. Institute of Medicine; 2009. PMID: None.

Figure 1. Past Month Cigarette Use Among Women Ages 15 to 44 Years, by Pregnancy Status: Combined Years 2002–2003 to 2011–2012



+ Difference between this estimate and the 2011-2012 estimate is statistically significant at the .05 level.

Source: 2012 National Survey on Drug Use and Health

Figure 2. Analytic Framework: Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation Among Adults and Pregnant Women

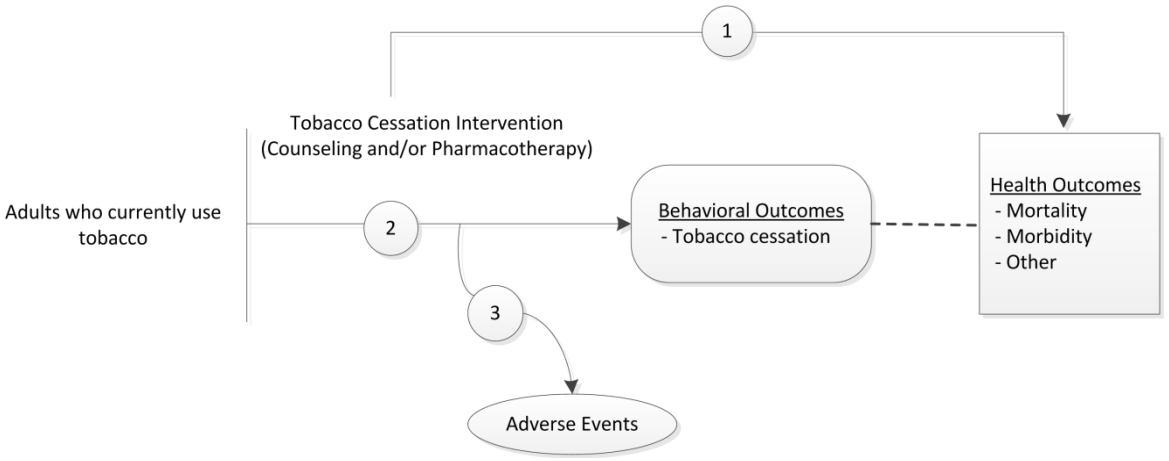


Table 1. Characteristics of Included Existing Systematic Reviews by Population, Intervention, and Last Search Date (k=54)

Population Intervention Category	Intervention Type	Name of Review	Quality Rating	Specific Intervention or Population	Last Search Date	Number of Included Studies	KQ1: Health Outcomes	KQ2: Cessation	KQ3: Harms
Adults Pharm-Efficacy ESR=6 (Primary=3)	NRT	*Stead, 2012a[140]	Good	NRT	July-12	150		X	
	Varenicline	*Cahill, 2012[154]	Good	Varenicline (Nicotine receptor partial agonists)	Dec-11	20		X	X
	Varenicline	Huang, 2012[120]	Good	Varenicline	Mar-11	10		X	X
	Bupropion SR	*Hughes, 2014[121]	Good	Bupropion SR (Antidepressants)	July-13	66		X	X
	All Pharm	Mills, 2012[129]	Fair	NRT, Bupropion SR, Varenicline	Jan-12	146		X	
	All Pharm	Tran, 2010[145]	Fair	NRT, Bupropion SR, Varenicline	Feb-09	143		X	X
Adults Pharm-Harms ESR=3 (Primary=3)	All Pharm Harms	*Mills, 2014[130]	Fair	NRT, Bupropion SR, Varenicline harms	Mar-13	63			X
	Varenicline Harms	*Prochaska, 2012[135]	Good	Varenicline harms	Sept-11	22			X
	NRT Harms	*Mills, 2010[128]	Fair	NRT harms	Nov-09	92			X
Adults Combined pharm and behavioral ESR=1 (Primary=1)	Combined pharm and behavioral	*Stead, 2012b[138]	Good	Combined pharmacotherapy and behavioral support	July-12	41		X	
Adults Behavioral ESR=26 (Primary=11)	Behavioral support as an adjunct to pharmacotherapy	*Stead, 2013a[142]	Good	Behavioral support as adjunct to pharmacotherapy	July-12	38		X	
	Behavioral support and counseling	*Rice, 2013[136]	Good	Nurse support	June-13	49		X	
		*Stead, 2013b[139]	Good	Physician advice	Jan-13	42	X	X	
		Carr, 2012[108]	Good	Interventions in dental settings	Nov-11	14		X	
		Cahill, 2010[106]	Good	Stage-based interventions	Aug-10	41		X	
		Hettema, 2010†[119]	Fair	Motivational interviewing	June-08	23		X	
		Lai, 2010[124]	Good	Motivational interviewing	NR-08	14		X	
		Bodner, 2009[103]	Fair	Health professional advice	NR	30		X	
		Mottillo, 2009[131]	Fair	Counseling	Aug-07	50		X	
	Print-based self-help materials	*Hartmann-Boyce, 2014[118]	Good	Print-based self-help materials	April-14	74		X	
	Telephone Counseling	*Stead, 2013c[141]	Good	Telephone counseling	May-13	77		X	
		*Whittaker, 2012[152]	Fair	Mobile phone	May-12	5		X	
		Tzelepis, 2011[147]	Fair	Proactive telephone counseling	Dec-08	24		X	
	Computer-based interventions	*Civljak, 2013[113]	Good	Internet-based	April-13	28		X	
		Brown, 2013[104]	Fair	Internet-based, young adults	Feb-11	8		X	
		Chen, 2012[111]	Good	Computer and electronic aids	Dec-09	60		X	
		Hutton, 2011[122]	Good	Internet-based	Dec-09	21		X	
		Myung, 2009[132]	Good	Internet- or computer-based	Aug-08	22		X	
		Shahab, 2009[137]	Fair	Internet-based	Dec-08	11		X	

Table 1. Characteristics of Included Existing Systematic Reviews by Population, Intervention, and Last Search Date (k=54)

Population Intervention Category	Intervention Type	Name of Review	Quality Rating	Specific Intervention or Population	Last Search Date	Number of Included Studies	KQ1: Health Outcomes	KQ2: Cessation	KQ3: Harms
	Biomedical risk assessment	*Bize, 2012[102]	Good	Biomedical risk assessment	June-12	15		X	
	Exercise	*Ussher, 2014[148]	Fair	Exercise	May-14	20		X	
	Complementary and alternative therapies	*White, 2014[151]	Good	Acupuncture	Oct-13	38		X	
		Di, 2014[114]	Good	Acupuncture	Jan-13	25		X	X
		Cheng, 2012[112]	Fair	Acupoint stimulation	Mar-11	20		X	
		Tahiri, 2012[144]	Fair	Alternative therapies	Dec-10	14		X	
		*Barnes, 2010[100]	Good	Hypnotherapy	July-10	11		X	X
Adults Electronic nicotine delivery systems‡ RCTs=2	Electronic nicotine delivery systems‡	Bullen, 2013[105]	Fair	Electronic cigarettes	NA	NA		X	X
		Caponnetto, 2013[107,107]	Fair	Electronic cigarettes	NA	NA		X	X
Specific Adult Subpopulations ESR=7 (Primary=0)	Behavioral	Liu, 2013[126]	Fair	Adapted interventions for ethnic minorities	April-13	28		X	
	Behavioral	Johnston, 2013[123]	Fair	Indigenous populations	May-12	5		X	
	Pharm and Behavioral	Zbikowski, 2012[153]	Fair	Older adults	June-11	13		X	
	Pharm and Behavioral	Carson, 2012[109]	Fair	Indigenous populations	April-11	4		X	X
	Pharm and Behavioral	Ebbert, 2011[115]	Good	Smokeless tobacco users	Oct-10	25		X	
	Behavioral	Nierkens, 2013[134]	Good	Adapted interventions for ethnic minorities	April-10	5		X	
	Behavioral	Villanti, 2010[150]	Fair	Young adults	Aug-09	14		X	
Pregnant Women ESR=8 (Primary=2)	Pharm	*Coleman, 2012[92]	Good	Pharm among pregnant women	Mar-12	6	X	X	X
	Pharm	Myung, 2012[133]	Good	Pharm among pregnant women	June-11	7	X	X	X
	Behavioral	*Chamberlain, 2013[110]	Good	Behavioral interventions among pregnant women	Mar-13	86	X	X	X
	Behavioral	Filion, 2011[116]	Fair	Behavioral interventions among pregnant women	June-10	8		X	
	Behavioral	Hettema, 2010†[119]	Fair	Behavioral interventions among pregnant women	June-08	8		X	
	Pharm and Behavioral	Likis, 2014[125]	Good	Pharm and behavioral interventions among pregnant women	Jan-13	59	X	X	X
	Pharm and Behavioral	Su, 2013[143]	Fair	Pharm and behavioral interventions among pregnant women	Dec-12	32		X	

Table 1. Characteristics of Included Existing Systematic Reviews by Population, Intervention, and Last Search Date (k=54)

Population Intervention Category	Intervention Type	Name of Review	Quality Rating	Specific Intervention or Population	Last Search Date	Number of Included Studies	KQ1: Health Outcomes	KQ2: Cessation	KQ3: Harms
	Pharm and Behavioral	Lumley, 2009[228]	Good	Pharm and behavioral interventions among pregnant women	June-08	72	X	X	X
Patients with Mental Health Conditions ESR=4 (Primary=2)	Pharm and Behavioral	*Van der Meer, 2013[149]	Good	Patients with current or past depression	April-13	49		X	
	Pharm and Behavioral	*Tsoi, 2013[146]	Good	Patients with schizophrenia	Oct-12	34	X	X	X
	Pharm and Behavioral	Gierisch, 2010[117]	Fair	Patients with depression	Mar-10	16		X	X
	Pharm and Behavioral	Banham, 2010[99]	Fair	Patients with severe mental illness	Jan-08	8	X	X	X

*Primary review that served as the basis for the main findings

†Review includes both adults and pregnant women and is listed twice in Table 1

‡The review of electronic nicotine delivery systems was not based on a review of reviews; we included two RCTs based on a primary search for evidence

Abbreviations: ESR = existing systematic review; k = number of studies; KQ = key question; NR = not reported; NRT = nicotine replacement therapy; Pharm = pharmacotherapy interventions; RCT = randomized controlled trial; SR = sustained release.

Table 2. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, Listed by Primary Review and Intervention Type

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
*Stead, 2012a[140] Good	NRT	Placebo; no treatment; or different doses of NRT or combinations of NRT	July-12	NRT: 150	NR	RCTs or quasi-RCTs	Adult smokers motivated to quit	Smoking abstinence; AEs	≥6 months	Any
*Hughes, 2014[121] Good	Antidepressants (Bupropion SR*)	Placebo; no treatment; or alternative pharm	July-13	Total: 90 Bupropion SR: 66	National Institute on Drug Abuse, NHS Research and Development Program	RCTs	Adult smokers	Smoking abstinence; AEs	≥6 months	Any
*Cahill, 2012[154] Good	Varenicline	Placebo; no treatment; or alternative pharm	Dec-11	Total: 24 Varenicline: 20	NHS Research and Development Fund	RCTs	Adult smokers	Smoking abstinence; AEs	≥6 months	Any
Huang, 2012[120] Good	Varenicline	Placebo or NRT	Mar-11	Varenicline: 10	NR	RCTs	Adult smokers	Smoking abstinence; AEs	≥12 months	Any
Mills, 2012[129] Fair	NRT, Bupropion SR, Varenicline	Placebo; no treatment; or alternative pharm	Jan-12	Total: 146 NRT: 87 Bupropion SR: 48 Varenicline: 11	Pfizer Ltd; Canadian Institutes of Health Research	RCTs	Adult smokers	Smoking abstinence	≥ 3 months	Any
Tran, 2010[145] Fair	NRT, Bupropion SR, Varenicline	Placebo or alternative pharm	Feb-09	Total: 143 NRT: 102 Bupropion SR: 23 Varenicline: 10 Combined: 11	Health Canada; government funded	RCTs	Adult smokers; special populations (e.g. pregnant women, mental illness, CVD)	Smoking abstinence; any treatment-related comorbidity; serious AEs	≥6 months	Any
*Mills, 2014[130] Fair	NRT, Bupropion SR, Varenicline	Placebo	Mar-13	Total: 63 NRT: 21 Bupropion SR: 28 Varenicline: 18	NR	RCTs	Adult smokers	Cardiovascular AEs	Any followup accepted	NR
*Mills, 2010[128] Fair	NRT	Placebo or standard of care	Nov-09	NRT: 92	Pfizer Ltd; Canadian Institutes of Health Research	RCTs & obser-vational studies	Adult smokers	AEs	≥1 month	Any

Table 2. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, Listed by Primary Review and Intervention Type

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
*Prochaska, 2012[135] Good	Varenicline	Placebo	Sept-11	Varenicline: 22	National Institute on Drug Abuse and the State of California Tobacco-Related Disease Research Program	RCTs	Adult smokers	Serious cardiovascular AEs	Within 30 days of treat-ment discon-tinuation	Any

*Review served as basis for primary finding
†Quasi-RCTS are those that use quasi-random methods of assignment including alternation, date of birth, or medical record number

Abbreviations: AE = adverse event; CVD = cardiovascular disease; NHS = National Health Service; NR = not reported; NRT = nicotine replacement therapy; Pharm = pharmacotherapy; RCT = randomized controlled trial; SR = sustained release.

Table 3. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, as Listed in Text

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/Provider Characteristics
Stead, 2012a[140]	NRT: 150	<50 to >3,500 (Median: 240)	Average age (range): 40-50; 1 trial in adolescents Sex (% female): Most trials had equal female and male participants. 1 trial in only males; 4 in only women; and 4 in only pregnant women. Race: Recruited African American smokers (k=2) SES: NR Comorbidities: -Alcohol-dependent participants or those with history of alcohol dependence (k=3) -History of cardiac disease (k=1)	Smoking status: Trials typically recruited people who smoked at least 15 cigs/day. Average number smoked per day was over 20/day in most studies.1 trial recruited relapsed smokers. Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	Nicotine gum (k=55) Transdermal nicotine patch (k=43) Oral nicotine tablet or lozenge (k=6) Choice of products offered (k=5) Intranasal nicotine spray (k=4) Nicotine inhaler (k=4) Oral spray (k=1) Patch and inhaler (k=1) Patch and lozenge (k=1)	Setting: Medical clinics, primary care, antenatal clinics, smoking clinics, hospitals, OTC community volunteers Providers: NR

Table 3. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, as Listed in Text

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/Provider Characteristics
Hughes, 2014[121]	Bupropion SR: 66	15 to 1524	Average age (range): 36 to 56; 2 studies included adolescents Sex (% female, range):16 to 100; 2 studies included males only Race: -Recruited African American smokers only (k=2) -Recruited Maori smokers only (k=1) SES: NR Comorbidities/other substance abuse: -Depression (current) (k=2) *Most of the bupropion SR trials excluded participants with current depression but not those with a history of depression. -COPD (k=3) -Schizophrenia (k=5) -PTSD (k=1) -Cancer (k=1) -Suspected tuberculosis (k=1) -Alcoholism (k=2) -CVD (k=4)	Smoking status: 5 to 37 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	66 studies included: -44 evaluated bupropion SR as a single pharmacotherapy to assist initial cessation -12 tested bupropion SR as an adjunct to NRT Other studies made direct comparisons between bupropion SR and NRT, bupropion SR and nortriptyline, bupropion SR and varenicline	Setting: Variety of health care settings including community-based clinics, outpatient clinics, cessation clinics, universities, and mental health clinics Providers: NR

Table 3. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, as Listed in Text

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/Provider Characteristics
Cahill, 2012[154]	Varenicline: 20 trials	32 to 1,202	Average age (range): 39 to 57 Sex (% female, range): 3 to 67 Race (% white, range): 68 to 93 SES: NR Comorbidities/other substance use: 1 study in smokers with schizophrenia or schizoaffective disorders; 2 studies included patients with CVD	Smoking status:19.6 to 28 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	20 RCTs of varenicline -15 double-blinded RCTS evaluated varenicline for smoking cessation -1 single-blinded RCT compared varenicline plus counseling with counseling alone in patients admitted to hospital for smoking-related acute illnesses -2 open-label RCTs compared varenicline with NRT but without a placebo arm -1 RCT evaluated varenicline as an aid to relapse prevention -1 RCT gave varenicline to all the participants but delivered behavioral support either online or by telephone or both	Setting: NR Providers: NR

Table 3. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, as Listed in Text

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/Provider Characteristics
Mills, 2010[128]	120	7 to 1,429 (RCTs) 22 to 65,599 (obs)	Average age: NR Sex (% female): NR (4 RCTs in pregnant women, 1 in postmenopausal women) Race: NR SES: NR Comorbidities/other substance use: -Conducted in populations with medical and psychiatric comorbidities (e.g., smoking-related diseases, chronic diseases, alcoholism, depression) (k=6) -Conducted in adult populations with medical comorbidities (k=2)	Smoking status: (observational studies) >10 to 35 (average cpd range) Nicotine dependence: (observational studies) Range: 1 to 50 yrs	Readiness to quit: In the majority of studies, participants were "planning on quitting." Quit history: NR consistently	Evaluated all types of NRT. 120 studies included. RCTs: 92 RCTs; 83 placebo controlled Patch (k=42) Gum (k=26) Spray (k=6) Inhaler (k=6) Tablet (k=4) Lozenge (k=1) NRT combination (k=35) *59 RCTs included co-interventions Counseling (k=20) Behavioral or psychological treatment (k=19) Advice (k=12) Education (k=3) Additional NRT/placebo (k=4) Rimonabant (appetite suppressant) (k=1) Observational: Patch (k=17) Spray (k=2) Gum (k=1) NRT combination (k=8) *Majority of obs studies included co-interventions Counseling (k=12) Behavior/behavior modification (k=3) Education (k=3) Self-help booklet (k=1)	Setting: NR Providers: NR

Table 3. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Efficacy and Adverse Events of Pharmacotherapy Tobacco Cessation Interventions Among Adults, as Listed in Text

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/Provider Characteristics
Mills, 2014[130]	63	32 to 3,296	Average age: 60.1 years Sex (% female, range): 0 to 100 Race: NR SES: NR Comorbidities/other substance use: -Patients with CVD (k=8) -Patients with COPD (k=4) -Perioperative patients (k=1)	Smoking status: ≥10 to 31 (average cpd range) Nicotine dependence: ≥1 to 51 years	Readiness to quit: NR consistently Quit history: NR consistently	63 trials included: -NRT vs placebo (k=19) -Bupropion SR vs placebo (k=27) -Varenicline vs placebo (k=18) -High-dose NRT vs placebo (k=1) -Combination NRT vs control (k=1) -Bupropion SR vs varenicline (k=2) -Bupropion SR vs NRT (k=3) -Varenicline vs NRT (k=1)	Setting: NR Providers: NR
Prochaska, 2012[135]	22	31 to 1,210 (median 404)	Average age: NR Sex (% female, range): 0 to 51 Race (% white, range): 0 to 99.3 SES: NR Comorbidities/other substance use: -Patients with current or past CVD (k=13)	Smoking status: 17.1 to 24.4 (average cpd range); mean 21.5 Nicotine dependence: 16.9 to 40.5 years; mean 25.1	Readiness to quit: NR consistently Quit history: NR consistently	22 trials included—all varenicline vs. placebo	Setting: NR Providers: NR

Abbreviations: cigs = cigarettes; COPD = Chronic Obstructive Pulmonary Disease; cpd = cigarettes per day; CVD = cardiovascular disease; k = number of studies; NR = not reported; NRT = nicotine replacement therapy; obs = observational; OTC = over the counter; RCT = randomized controlled trial; SES = socioeconomic status; SR = sustained release; yrs = years.

Table 4. Summary of Tobacco Abstinence Results (KQ 2) From Reviews of Pharmacotherapy Tobacco Cessation Interventions Among Adults

Review, Year	Intervention	Control	k	N	Abstinence Measures*	Followup	IG Events	IG N	IG Quit Rate†	CG Events	CG N	CG Quit Rate†	Risk Ratio‡	95% CI	I^2
Stead, 2012a[140]	NRT, all forms	Placebo or no NRT‖	117	51,265	57% CA 87% BV	≥6 months§	4,704	27,258	17.3%	2,466	24,007	10.3%	1.60	1.53, 1.68	30%
	NRT, gum		56	22,581	55% CA 82% BV	≥6 months§	1,732	10,596	16.3%	1,196	11,985	10.0%	1.49	1.40, 1.60	40%
	NRT, patch		43	19,586	58% CA 88% BV	≥6 months§	1,873	11,746	15.9%	766	7,840	9.8%	1.64	1.52, 1.78	19%
	NRT, tablets/ lozenges		7	3,405	29% CA 100% BV	≥6 months§	337	1,808	18.6%	134	1,597	8.4%	1.95	1.61, 2.36	24%
	Two forms of NRT (dual)	One form of NRT	9	4,664	67% CA 89% BV	≥6 months§	368	1,785	20.6%	448	2,879	15.6%	1.34	1.18, 1.51	34%
Hughes, 2014[121]	Bupropion SR	Placebo or no bupropion SR¶	44	13,728	77% CA 95% BV	≥6 months	1,507	7,646	19.7%	701	6,082	11.5%	1.62	1.49, 1.76	18%
			17	3,862	59% CA 100% BV	6 months	483	2,202	21.9%	200	1,660	12.0%	1.69	1.45, 1.97	0%
			27	9,866	81% CA 93% BV	12 months	1024	5,444	18.8%	501	4,422	11.3%	1.59	1.44, 1.76	39%
Cahill, 2012[154]	Varenicline	Placebo#	14	6,166	100% CA 100% BV	≥6 months§	954	3,412	28.0%	331	2,754	12.0%	2.27	2.02, 2.55	63%

* Used strictest available criteria to define abstinence (i.e., continuous, sustained, or prolonged abstinence was preferred over point prevalence abstinence and biochemically validated rates were used where available). "Continuous abstinence" reflects reviews that reported outcomes as continuous (completely abstinent from quit date with 0-5 cigarettes during that time), "sustained" abstinence (not defined), or prolonged abstinence (allowing a grace period following the quit date to allow for lapses).

† Weighted average quit rate

‡Pooled risk ratios estimated using the Mantel-Haenszel fixed-effects model

§ Longest followup time point reported

‖ The control group in 25/117 trials did not have a matched placebo control; findings were not sensitive to the exclusion on non-placebo controlled studies

¶ The control group in 3/44 trials did not have a matched placebo control.

#The control group in 1/14 included trials did not have a matched placebo control; a sensitivity analysis excluding it made no appreciable difference to the overall estimate.

Abbreviations: BV = biochemically verified; CA = continuous abstinence; CI = confidence interval; CG = control group; IG = intervention group; k = number of studies; N = number; NRT = nicotine replacement therapy; SR = sustained release.

Table 5. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
*Stead, 2012b[138] Good	Combined pharm and behavioral interventions	Usual care, self-help materials, brief advice, or less intensive behavioral support	July-12	41	NHS, National Institute of Health Research	RCTs or quasi-RCTs	Nonpregnant adult smokers	Smoking abstinence	≥6 months	Any
*Stead, 2013a[142] Good	Behavioral interventions as adjuncts to pharmacotherapy	Any behavioral support of lower intensity	July-12	38	NHS National Institute for Health Research	RCTs or quasi-RCTs	Nonpregnant adult smokers	Smoking abstinence	≥6 months	Any
*Rice, 2013[136] Good	Nurse delivered behavioral support	Varying types of "usual care" or low-intensity support	June-13	49	American Heart Association; NHS Research & Development Program	RCTs	Nonpregnant adult smokers	Smoking abstinence	≥6 months	Any
*Stead, 2013b[139] Good	Physician advice	No advice, usual care, or differing levels of physician advice	Jan-13	42	NHS Research and Development Program	RCTs or quasi-RCTs	Nonpregnant adult smokers	Smoking abstinence	≥6 months	Any
Carr, 2012[108] Good	Any tobacco cessation intervention in dental setting	Usual care, placebo, or other intervention	Nov-11	14	National Institute for Dental and Craniofacial Research, US	RCTs or pseudo-RCTs	Tobacco users of any age	Tobacco abstinence	≥6 months	Dental setting or dental provider in community
Cahill, 2010[106] Good	Stage-based	Non-stage-based intervention of lower or equal intensity; no intervention; or usual care	Aug-10	41	NR	RCTs or quasi-RCTs	Smokers of any age, race or gender	Smoking abstinence; adverse events	≥6 months from start of treatment	Any
Hettema, 2010[119] Fair	Motivational interviewing	Non-MI	June-08	Total: 31 (non-pregnant: 23)	NR	RCTs	Pregnant and nonpregnant smoking adults	Smoking abstinence	Short term (≤6 months) or long term (≥6 months)	Any
Lai, 2010[124] Good	Motivational interviewing	Brief advice; low-intensity intervention; or usual care	April-09	14	NR	RCTs	Nonpregnant adult smokers	Smoking abstinence	≥6 months	Any
Bodner, 2009[103] Fair	Smoking cessation advice by a health professional	Usual care or no advice	NR	30	CIHR Institute of Musculoskeletal Health and Arthritis; Canadian Lung Association	RCTs or quasi-experime-ntal studies	Adult smokers	Smoking abstinence	≥5 months post-intervention	Any

Table 5. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
Mottillo, 2009[131] Fair	Behavioral (brief advice, individual, group, and telephone counseling)	Usual care	Aug-07	50	Canadian Institutes of Health Research	RCTs	Adult smokers	Smoking abstinence	6 or 12 months	Any
*Hartmann-Boyce, 2014[118] Good	Print-based self-help materials	No treatment or other minimal contact strategies	April-14	74	NHS Research & Development Programme	RCTs or quasi-RCTs	Adult smokers	Smoking abstinence	≥6 months	Any
*Stead, 2013c[141] Good	Telephone counseling	Minimal intervention (standard self-help materials or brief advice)	May-13	77	NHS Research & Development Program	RCTs or quasi-RCTs	Adult smokers	Smoking abstinence	≥6 months	Any
*Whittaker, 2012[152] Fair	Mobile phone-based intervention	Control (various)	May-12	5	National Institute for Health Innovation, New Zealand; Cancer Council Victoria, Australia	RCTs or quasi-RCTs	Smokers of any age	Smoking abstinence	≥6 months	Any
Tzelepis, 2011[147] Fair	Telephone counseling	Self-help materials/no intervention	Dec-08	24	Cancer Council New South Wales; University of Newcastle	RCTs	Adult smokers	Smoking abstinence	≥6 months	Any
*Civljak, 2013[113] Good	Internet-based	No intervention; different Internet intervention; or non-Internet intervention	April-13	28	NHS Connecting for Health Evaluation Programme; NHS Research and Development Programme	RCTs or quasi-RCTs	Smokers of any age (studies in adolescents and young adults analyzed separately)	Smoking abstinence	≥6 months (studies with shorter FU were included and reported narratively)	Any
Brown, 2013[104] Fair	Technology based	Not clearly stated	Feb-11	8	NR	RCTs, quasi-RCTs and cohort studies	Young adult (ages 18-30 years) smokers recruited from U.S. colleges or university campuses	Smoking abstinence	≥6 months preferred, shorter followups accepted	Any

Table 5. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
Chen, 2012[111] Good	Computer, internet, mobile telephone, or other electronic	No intervention; standard self-help materials	Dec-09	60	HTA program	RCTs or quasi-RCTs	Adult smokers	Smoking abstinence	≥6 months	Any
Hutton, 2011[122] Good	Web-delivered	Control (various)	Feb-10	21	International Union Against Tuberculosis and Lung Disease	RCTs	Smoking adolescents, college students, and adults	Smoking abstinence	≥1 month	Any
Myung, 2009[132] Good	Web- or computer-based	Usual care	Aug-08	22	CDC	RCTs	Adult smokers	Smoking abstinence	>3 months	Any
Shahab, 2009[137] Fair	Internet-based (must make use of the interactive nature of the internet)	Minimal control condition (e.g. booklet or static website) or waitlist control	Dec-08	11	Department of Health, England	RCTs	Adult smokers	Smoking abstinence	≥1 month	Any
*Bize, 2012[102] Good	Biomedical risk assessment	No biomedical risk assessment control	June-12	15	NR	RCTs	Adult smokers who participated in smoking cessation programs, screening for respiratory disease, or health checkups	Smoking abstinence	≥6 months	Any
*Ussher, 2014[148] Fair	Exercise-based interventions	Smoking cessation program alone	May-2014	20	NR	RCTs	Adult smokers wishing to quit or recent quitters	Smoking abstinence	≥6 months	NR

Table 5. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
*White, 2014[151] Good	Acupuncture, acupressure, laser therapy, or electrostimulation	No intervention; sham acupuncture (i.e., acupuncture to known spots that aren't related to smoking cessation); usual care; placebo; other intervention (e.g., locked cigarette case controlled by time switch)	Oct-13	38	Universities of Exeter and Plymouth, UK; National Research Centre for Complementary Medicine, Norway; NHS Research and Development National Cancer Program	RCTs	Adult tobacco smokers wishing to stop smoking	Smoking abstinence	Short-term: up to 6 weeks from the quit date Long-term: 6 to 12 months from quit date	Any
Di, 2014[114] Good	Ear acupuncture/ acupressure or auriculotherapy	Nonspecific/ inactive control or other smoking cessation intervention	Jan-13	25	Guangdong Provincial Academy of Chinese Medical Sciences	RCTs or quasi-RCTs	Smokers aiming to quit	Smoking abstinence	Any	Any
Cheng, 2012[112] Fair	Acupoint stimulation with or without NRT	Nontreatment, placebo acupuncture, placebo acupressure, or medication	Mar-11	20	NR	RCTs	Not clearly defined	Smoking abstinence; smoking reduction	Earliest and last measured timepoints and at 3- and 6-month followups	Any
Tahiri, 2012[144] Fair	Alternative smoking cessation aids (acupuncture, hypnotherapy, aversive smoking)	No alternative smoking cessation aid	Dec-10	14	Canadian Institutes of Health Research	RCTs	Adult smokers	Smoking abstinence	6 or 12 months	Not clearly stated, but clinic administered alternative smoking cessation aid implied
*Barnes, 2010[100] Good	Hypnotherapy	No treatment or any other therapeutic intervention	July-10	11	Wellcome Trust, UK; NHS Research and Development National Cancer Program	RCTs	Tobacco smokers wishing to stop smoking	Smoking abstinence	≥6 months	NR

*Review served as basis for main finding
†Quasi-RCTS are those that use quasi-random methods of assignment including alternation, date of birth, or medical record number.

Abbreviations: AE = adverse event; CDC = Centers for Disease Control and Prevention; CIHR = Canadian Institutes of Health Research; HTA = Health Technology Assessment; NHS = National Health Service; NR = not reported; NRT = nicotine replacement therapy; Pharm = pharmacotherapy; RCT = randomized controlled trial; UK = United Kingdom; US = United States.

Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
Stead, 2012b[138]	41	15 to 5,887	Average age: "low 40s to mid-50s" Sex (% female): 35 to 65; recruited only women (k=2); only men (k=1) Race: NR SES: NR, but 1 study recruited residents of low-income public housing departments Comorbidities/other substance use: -Outpatient substance abuse treatment programs (k=2) -Mental health service settings (k=2) -AIDS clinic (k=1) -Cancer patients (k=2) -Cancer survivors (k=1) -Chinese men w/erectile dysfunction (k=1) -COPD or mild airway obstruction (k=3)	Smoking status: 12 to 31 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: -Motivation required (k=18) -Motivation not required but participants likely to have been interested in quitting (k=10) -Not selected by motivation (k=13) Quit history: NR consistently	Included 41 studies. Typical intervention involved multiple contacts with a specialist cessation advisor or counselor, with most participants using some pharmacotherapy and receiving multiple contacts. Some interventions involved making pharmacotherapy and behavioral components available to a large population in which takeup of treatment was low (k=1), or providing a brief intervention to all participants and offering stepped care for those willing to set a quit date (k=2), or an intervention delivered entirely by mail or prerecorded phone messages (k=1), or telephone counseling alone (k=1); all others included some face-to-face contact but additional sessions were sometimes provided by telephone. >50% of RCTs offered between 4 and 8 sessions and around 25% >8 sessions. The modal category for contact time was 91 to 300 min, with 10 RCTs offering between 31 and 90 min and 7 RCTs offering >300 min. The control group typically received brief advice and self-help materials.	Setting: High proportion of trials conducted in health care settings and/or recruited people with specific health needs Settings included: Hospital inpatient (k=8) Primary care clinics (k=6) Awaiting admission for surgery (k=4) Dental clinics (k=2) Mental health service settings (k=2) AIDS clinic (k=1) Annual occupational health checks (k=1) Members of HMOs (k=1) Low income public housing department (k=1) VA medical center (k=1) Providers: Mostly specialist cessation counselors or trained trial personnel; in a small subgroup, intervention was provided by general practitioners/ family physicians (k=3), dentists or dental hygienists (k=2), occupational physicians (k=1), peer group counselors (k=2), or trained lay advisors (k=1)

Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
Stead 2013a[142]	38	69 to 4,614	Average age (range): 33 to 61 Sex (% female): 12 to 100; 2 studies enrolled only females Race: NR SES: NR Comorbidities/other substance use: NR	Smoking status: >4 to 30.5 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: Majority recruited volunteers who were interested in making a quit attempt Quit history: NR consistently	-Nicotine patch (k=19) -Nicotine gum (k=6) -Sublingual tablets (k=1) -Not specified (k=1) -Bupropion SR (k=3) -Nortriptyline alone (k=1) -Varenicline alone (k=1) -NRT or bupropion SR (k=3) -Bupropion SR or nortriptyline (k=1) -NRT and bupropion SR (k=2) Intensity of behavioral support greatly varied for both intervention and control groups; in 6 studies there was no personal contact for the controls; in 16 studies the control arms had between 1 and 3 contacts (which could be face-to face or by telephone) and most of these had a total contact duration of between 4 and 30 minutes; in 14 studies there were 4 to 8 contacts scheduled for the controls, and these typically had a total contact time of 91 to 300 min	Setting: -Primary care (k=4) -Chest clinic (k=1) -CVD outpatient clinic (k=1) -HIV clinic (k=1) -Mental health clinics (k=1) -Substance abuse clinics (k=2) -VA hospital (k=1) -HMO (k=4) -Community (k=23) Providers: NR
Rice, 2013[136]	49	40 to 12,472	Average age (range): 33 to 61 Sex (% female): NR consistently; women only (k=3); men only (k=1) Race: NR SES: NR Comorbidities/other substance use: -Diagnosed cardiovascular health problems (k=15) -Judged to be at high risk of developing heart disease (k=1)	Smoking status: Variable, cigarettes per day reported for a subset of studies Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	35/49 studies with a total of over 17,000 participants contributed to the main comparison of nursing interventions vs control (28 were classified as high intensity and 7 classified as low intensity) 7/49 examined a smoking cessation intervention as a component of multiple risk factor reduction interventions in adults with CVD. 4/49 had a smoking cessation component that was clearly defined, of high intensity, and independently measurable.	Setting: -Hospital (k=20) -Primary care (k=26) -Worksite (k=1_ -Community (k=2) Providers: -Of the high intensity intervention studies, 12 used nurses for whom the intervention was a core component of their role. -In 9 studies the intervention was delivered by a nurse specifically employed by the project -Four studies intensive

Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
			-Respiratory diseases (k=2) -Diabetes (k=1) -Surgical patients (k=2) -Head and neck cancer patients (k=1)			3/49 had a smoking cessation component that was not clearly specified.	interventions were intended to be delivered by nurses for whom it was not a core task -Most of the low intensity interventions were delivered by primary care or outpatient clinic nurses
Stead, 2013b[139]	42	60 to 3,215	Average age: NR Sex (% female): NR; 1 trial recruited males only Race: NR SES: NR Comorbidities/other substance use: NR consistently	Smoking status: ≥1 to ≥25 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	42 RCTs included: -Minimal advice vs. no advice (k=17) -Intensive intervention vs. control (k=11) -Intensive intervention vs. minimal intervention (k=14) -2 intensive interventions (k=1) -Intervention based on the 4 As model (k=1)- Advice vs. computer-tailored letters (k=2) Some studies tested variations in interventions and contributed to more than 1 comparison. The definition of what constituted 'advice' varied considerably.	Setting: Mostly family/ general practice, but also government clinic, adult diabetic outpatient clinic, hospital cardiac unit, worksite, and community settings Providers: Health care personnel (e.g., medical registrar, physicians, hospital consultants)
Hartmann-Boyce, 2014[118]	74	40 to 6697	Average age (range): 34 to 72 Sex (% female): 8 to 75 Race: NR SES: NR Comorbidities/other substance abuse: -Cardiovascular health issues (k=1)	Smoking status: ≥5 to 31 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: Interest in quitting was not a selection criteria, however smokers recruited to trials ranged from those who had already succeeded in quitting for 48 hours to those with no interest in quitting Quit history: NR consistently	74 trials included: - Standard self-help materials vs. no intervention or provided standard materials as an adjunct to advice (k=34) -Targeted or tailored self-help methods vs. no targeting/tailoring or other variations of programs (k=40) The content and format of the self-help programmes were varied. The most frequently used approach was the American Lung Association *Freedom from smoking in 20 days* cessation manual and *A lifetime of freedom from smoking* maintenance manual.	Setting: NR Providers: NR

Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
Stead, 2013c[141]	77	40 to 7,354 (median: 820)	Average age: "Participants were predominantly older adults with an average age typically in the 40s." Sex (% female): Only women (k=5); only men (k=4) Race: -Culturally tailored intervention for Chinese, Korean and Vietnamese smokers (k=1) -Intervention focused on Arabic smokers (k=1) SES: NR Comorbidities/other substance abuse: -CVD (k=2)	Smoking status: ≥1 to 28 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: -Recruited smokers who wanted to make a quit attempt (k=16) -Did not state that participants were included on the basis of motivation, although relatively high proportions may have been interested in quitting (k=35) Quit history: NR consistently	77 included studies -Interventions for smokers who contacted a quitline/helpline (k=15) -Providing access to a helpline (k=3) -Proactive counseling not initiated by calls to quitlines (k=51) -Other (k=8)	Setting: Variable. "Most of the studies were trials of proactive calls from a counselor, or from an automated interactive voice response system." 3 studies recruited participants in health care settings and referred them to services provided by quitlines." Providers: Majority of interventions were administered by professional counsellors or health care providers trained to offer advice over the telephone

Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
Whittaker, 2012[152]	5	200 to 5,800	Average age (range): 22 to 42 Sex (% female): 45 to 63 Race: NR SES: NR Comorbidities/other substance use: NR	Smoking status: 15 to 20 (average cpd range) Nicotine dependence: Participants in most of the studies had similar degrees of nicotine dependence, with mean FTND scores of 5 in one trial and 60% of participants in another trial scoring ≤5. However, in a third trial the Hooked on Nicotine Checklist mean scores of 8 indicated a highly addicted group.	Readiness to quit: 4/5 trials recruited participants ready or interested in quitting, or willing to quit in the next month Quit history: NR consistently	3/5 trials were based on the same intervention program, which involved participants setting a quit day within 3 weeks and then receiving an automated personalized program of regular text messages. 1/5 trial involved a web-based Quit Coach and a text messaging intervention. 1/5 trial implemented a video messaging intervention.	Setting: NA; all interventions were strictly mobile phone based Providers: NA; all interventions were strictly mobile phone based
Civlijak, 2013[113]	28	<150 to ~12,000	Average age (range): 16 to 57 Sex (% female): "more women than men" Race: NR consistently SES: NR Comorbidities/other substance use: NR	Smoking status: ≥1 to 40 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: Recruitment was largely web-based, with participants finding the sites through search engines and browsing. As a result of these methods, participants included in these trials were smokers motivated to quit, who chose the internet as a tool for smoking cessation support. Quit history: NR consistently	28 included studies: -Active Internet intervention vs. non-Internet arm (k=15) -Compared 2 Internet interventions (k=14) *1 study contributes to both categories* A range of internet interventions were tested in the included studies, from a very low intensity intervention providing a list of websites for smoking cessation to highly intensive interventions consisting of Internet-, email- and mobile phone-delivered components. Tailored internet interventions differed in the amount of tailoring,	Setting: Recruited smokers from health care settings (k=5); remaining trials used web-based recruitment Providers: Not applicable since interventions were provided via the internet

Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
						from a bulletin board facility, a multimedia component, tailored and personalized access to very high-depth tailored stories and highly personalized message sources.	
Bize, 2012[102]	15	90 to 2,110	Average age (range): 32 to 53 Sex (% female, range): 4 to 63 Race: NR SES: NR Comorbidities/other substance use: NR	Smoking status: 11.9 to 29.2 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	Of the 16 interventions: -Exhaled CO measurements (k=4) -Combination of exhaled CO measurement and spirometry (k=4) -Spirometry alone (k=3) -Ultrasonography of carotid arteries with photographic demonstration of atherosclerotic plaques when present (k=2) -Feedback about genetic susceptibility to cancer (k=3)	Setting: -General practice (k=5) -Outpatient clinics (k=4) -'Smoking clinic' (k=2) -Health promotion clinic for army veterans (k=1) -Company (workplace) (k=1) -Research institutions (k=2) Providers: -Physician (k=4) -Nurse (k=4) -Specific study staff member (k=6) -Trained health educator in 1 trial (k=1)
Ussher, 2014[148]	20	20 to 2,318	Average age (range): 17 to 59 Sex (% female): only women (k=9); only men (k=1) Race: "13 studies recorded ethnic status, and all reported a predominantly white sample." SES: NR Comorbidities/other substance use: -Recruited post-acutemyocardial infarction patients (k=1)	Smoking status: >10 to 32 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: All studies recruited smokers wishing to quit or were recent quitters Quit history: NR consistently	In all but 2 of the studies, a multi-session cognitive behavioral smoking cessation program was provided for intervention and control conditions. In 10 studies this began prior to quit day. 1 study provided only a single session cessation program and participants were post-acute myocardial infarction patients, with the intervention being for relapse prevention. 1 study delivered a smoking cessation program via the Internet and this was only available for the nonexercise condition. 6 studies included nicotine patches as part of the smoking cessation program, 1 study used nicotine gum, and 3 promoted NRT in general.	Setting: NR Providers: NR

Table 6. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy of Behavioral Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
						Most of the trials employed supervised, group-based cardiovascular-type exercise supplemented by a home-based program.	
White, 2014[151]	38	18 to 651	Average age (range): NR consistently Sex (% female): NR consistently Race: NR SES: NR Comorbidities/other substance use: NR	Smoking status: NR consistently Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	38 included studies: -Acupuncture (k=23) -Acupressure (k=5) -Laser stimulation (k=3) -Electrostimulation (k=7) 12 studies also used continuous auricular stimulation in combination with acupuncture, acupressure or electrostimulation.	Setting: NR Providers: NR
Barnes, 2010[100]	11	20 to 286	Average age (range): 30 to 40 Sex (% female): "more females than males" Race: NR SES: NR Comorbidities/other substance use: NR	Smoking status: 20 to 40 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	RCTs varied in the method of hypnotic induction used, number of sessions, and duration of treatments. The number of hypnotherapy sessions reported ranged from 1 to 8 sessions. The total duration of hypnosis used ranged from 30 min to 8 hours. 5 RCTs provided hypnotherapy in a group format.	Setting: NR Providers: NR

Abbreviations: AIDS = autoimmune deficiency syndrome; CO = carbon monoxide; COPD = Chronic Obstructive Pulmonary Disease; cpd = cigarettes per day; CVD = cardiovascular disease; FTND = Fagerstrom Test for Nicotine Dependence; HIV = human immunodeficiency virus; HMO = health maintenance organization; k = number of studies; min = minutes; NA = not applicable; NR = not reported; NRT = nicotine replacement therapy; RCT = randomized controlled trial; SES = socioeconomic status; SR = sustained release; VA = veterans administration.

Table 7. Summary of Tobacco Abstinence Results (KQ 2) From Reviews of Behavioral Counseling Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Intervention	Control	k	N	Abstinence Measures*	Followup§	IG Events	IG N	IG Quit Rate†	CG Events	CG N	CG Quit Rate†	Risk Ratio‡	95% CI	I^2
Stead, 2012b[138]	Combined pharm and behavioral interventions	Control (various)	40	15,021	56% CA 76% BV	≥6 months	1,134	7,810	14.5%	597	7,211	8.3%	1.82	1.66, 2.00	40%
Stead, 2013a[142]	Behavioral support as an adjunct to pharmaco-therapy	Pharmaco-therapy (any)	39	15,506	28% CA 79% BV	≥6 months	1,640	7,659	21.4%	1,438	7,847	18.3%	1.16	1.09, 1.24	3%
Rice, 2013[136]	Nursing interventions	Usual care or minimal intervention	35	17,604	29% CA 77% BV	≥6 months	1,273	9,589	13.3%	906	8,015	11.3%	1.29	1.20, 1.39	50%
Stead, 2013b[139]	Physician advice	No advice/ usual care	28	22,239	43% CA 36% BV	≥6 months	1,008	12,583	8.0%	462	9,656	4.8%	1.76	1.58, 1.96	40%
Hartmann-Boyce, 2014[118]	Nontailored self-help print materials	Control (various)	33	29,495	42% CA 55% BV	≥6 months	1,080	15,635	6.9%	891	13,860	6.4%	1.06	0.98, 1.16	23%
	Tailored self-help materials	Control (various)	32	40,890	72% CA 25% BV	≥6 months	1,502	21,017	7.1%	1,144	19,873	5.8%	1.28	1.18, 1.37	32%
Stead, 2013c[141]	Proactive telephone counseling in quitline callers	Control (various)	12	30,182	75% CA 17% BV	≥6 months	1,980	18,428	10.7%	895	11,754	7.6%	1.41‖	1.20, 1.66	NR
	Proactive telephone counseling (no quitline)	Control (various)	52	30,246	33% CA 35% BV	≥6 months	2,031	15,478	13.1%	1,433	14,768	9.7%	1.27	1.20, 1.36	42%
Whittaker, 2012[152]	Mobile phone interventions	Control (various)	5	9,100	Pooled results not presented given small number of studies and considerable heterogeneity (I^2=79%); results reported narratively										
Civljak, 2013[113]	Internet-based interventions	No treatment or other noninternet based treatments	23	>45,000	Pooled results not presented given small number of studies in subgroup analyses and considerable statistical heterogeneity; results will be reported narratively										
Bize, 2012[102]	Biomedical risk assessment	Control (various)	15	8,115	Pooled results not presented given small number of studies in each subgroup and substantial statistical heterogeneity; results reported narratively										

Table 7. Summary of Tobacco Abstinence Results (KQ 2) From Reviews of Behavioral Counseling Tobacco Cessation Interventions Among Adults, by Type of Intervention

Review, Year	Intervention	Control	k	N	Abstinence Measures*	Followup§	IG Events	IG N	IG Quit Rate†	CG Events	CG N	CG Quit Rate†	Risk Ratio‡	95% CI	I^2
Ussher, 2014[148]	Exercise alone or as adjunct to smoking cessation intervention	Smoking cessation intervention alone or usual care	20	5,870	No meta-analysis conducted due to small number of studies, small sample sizes and differences in study design and intervention; results reported narratively										
White, 2014[151]	Acupuncture	Sham acupuncture	9	1,892	33% CA 33% BV	6-12 months	122	997	12.2%	97	895	10.8%	1.10	0.86, 1.40	23%
Barnes, 2010[100]	Hypnotherapy	Brief advice/ advice	5	363	Pooled results not presented given small number of studies and clear asymmetry of the results of the included trials, indicating potential publication bias.										

* Used strictest available criteria to define abstinence (i.e., continuous, sustained, or prolonged abstinence was preferred over point prevalence abstinence and biochemically validated rates were used where available). "Continuous abstinence" reflects reviews that reported outcomes as continuous (completely abstinent from quit date with 0-5 cigarettes during that time), "sustained" abstinence (not defined), or prolonged abstinence (allowing a grace period following the quit date to allow for lapses).
† Weighted average quit rate
‡ Pooled risk ratios estimated using the Mantel-Haenszel fixed-effects model, unless otherwise noted
§ Longest followup time point reported
ǁ Results from sensitivity analysis using a random-effects model given substantial heterogeneity of fixed effects model (71%)

Abbreviations: BV = biochemically verified; CA = continuous abstinence; CI = confidence interval; CG = control group; IG = intervention group; k = number of studies; N = number; NR = not reported.

Table 8. Inclusion Criteria of Reviews on the Efficacy and Safety of Pharmacotherapy Tobacco Cessation Interventions Among Specific Adult Subpopulations, by Alphabetical Order

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
Carson, 2012[109] Fair	Pharm, cognitive and behavioral therapies, alternative therapies, public policy, and combination therapy	Usual care, minimal or no intervention, placebo	April-11	4	NR	RCTs or quasi-RCTs	Young people and adults of any age and either sex, who were Indigenous to their country and were active smokers participating in a smoking cessation study	Smoking abstinence	≥6 months	Any
Ebbert, 2011[115] Good	Pharm or behavioral	Usual care, placebo, or less intensive intervention	Oct-10	25	NR	RCTs or pseudo-RCTs	Smokeless tobacco users	Tobacco abstinence	≥6 months	Any
Johnston, 2013[123] Fair	Behavioral	Usual care	May-12	5	National Health and Medical Research Council of Australia; Health Research Council of New Zealand; James Russell Lewis Trust, New Zealand	RCTs, CCTs	Nonindigenous and indigenous adult smokers from Australia, New Zealand, United States, or Canada	Smoking abstinence	Not clearly stated	NR
Liu, 2013[126] Fair	Behavioral (culturally adapted interventions)	Usual care or nonadapted intervention	April-13	28	Medical Research Council, UK	RCTs, CCTs	Children and nonpregnant adult smokers of African-, Chinese- or South Asian-origin	Smoking abstinence	Not clearly stated	Not clearly stated but generally community-based
Nierkens, 2013[134] Good	Behavioral (culturally adapted interventions)	Same intervention without the cultural adaptation	April-10	5	Department of Public Health of the Academic Medical Center/University of Amsterdam	RCTs or non-RCTs	Adult ethnic minority population living in a high-income society	Smoking abstinence	≥1 month	Not clearly stated

Table 8. Inclusion Criteria of Reviews on the Efficacy and Safety of Pharmacotherapy Tobacco Cessation Interventions Among Specific Adult Subpopulations, by Alphabetical Order

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
Villanti, 2010[150] Fair	Pharm or behavioral	No intervention, delayed intervention after the last date of followup, information or education on smoking cessation, and general tobacco education or general health education	Aug-09	14	Doctoral training program by the Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, and the Maryland Cigarette Restitution Fund Research Grant to the Johns Hopkins Medical Institutions	Individual or group RCTs, controlled trials, quasi-experi-mental studies, and cohort studies	Smoking young adults (aged 18-24 years); light and intermittent smokers included	Smoking abstinence	>1 month	Not clearly stated but included colleges/ universities
Zbikowski, 2012[153] Fair	Behavioral and pharm	Not clearly stated	June-11	13	NR	Clinical trials, random-ized trials, and CCTs	Smokers aged ≥50 years	Smoking abstinence	Not clearly stated	Any

†Quasi-RCTS are those that use quasi-random methods of assignment including alternation, date of birth, or medical record number.

Abbreviations: CCT = case-control trial; NR = not reported; pharm = pharmacotherapy; RCT = randomized controlled trial; UK = United Kingdom.

Table 9. Efficacy and Safety of the Use of Electronic Nicotine Delivery Systems for Smoking Cessation

Study	Study Design Country	Sample Size, n	Population	Intervention	Control	Tobacco Cessation Outcomes	Other Outcomes	Adverse Events
Bullen, 2013[105]	RCT New Zealand	Total: 657 IG: 289 CG1: 295 CG2: 73	Age ≥18 years, had smoked ≥10 cigarettes per day for at least the past year, wanted to stop smoking	IG: Elusion e-cig (16 mg nicotine) + voluntary quitline behavioral support Duration: From 1 week before until 12 weeks after chosen quit date	CG1: NRT patch (21 mg nicotine per 24 hours) CG2: placebo e-cigs + voluntary quitline behavioral support	Continuous abstinence at 6 months post quit date (allowing ≤5 cigarettes); biochemically verified: IG: 7.3% CG1: 5.8% CG2: 4.1% *No statistically significant differences between groups 1- and 3-month cessation rates also did not differ	Median time to relapse: IG: 35 days (95% CI: 15, 56) CG1: 14 days (95% CI: 8,18)* CG2: 12 days (95% CI: 5, 34) *P<0.0001 Mean (SE) cigarette consumption at 6 months among those smoking ≥1 cigarette in past 7 days: IG: 9.7 (0.4) CG1: 7.7 (0.4) P=0.002	No serious events in any groups were related to product use
Caponnetto, 2013[107] EffiCiency and safety of an eLectronic cigAreTte (ECLAT)	RCT Italy	Total: 300 IG1: 100 IG2: 100 CG: 100	Ages 18–70 years, had smoked ≥10 cigarettes per day for at least the past 5 years, not currently attempting to quit smoking or wishing to do so in the next 30 days	Categoria 401 e-cig IG1: 12 weeks of 7.2 mg nicotine cartridges used *ad libitum* IG2: 6 weeks of 7.2 mg nicotine cartridges and 6 weeks of 5.4 mg nicotine cartridges used *ad libitum* Baseline visit and 8 followup visits (2-, 4-, 6-, 8-, 10-, 12-, 24-, 52-weeks)	Categoria 401 e-cig CG: 12 weeks of no-nicotine cartridges used *ad libitum*	Abstinence (not even a puff) since previous study visit; biochemically verified: 24 weeks IG1: 12.0% IG2: 10.0% CG: 5.0% Difference NR 52 weeks IG1: 13.0% IG2: 9.0% CG: 4.0% *Significant difference between IG1 and IG2 (11.0%) and CG (4.0%) (p=0.04)	Self-reported number of cig/day: Significant reduction in median value in all 3 groups at each time point; no between-group differences at 12, 24, or 52 weeks	No difference in frequency of adverse events among study groups at each time point

Abbreviations: CG = control group; CI = confidence interval; cig = cigarette; e-cig = electronic cigarette; IG = intervention group; mg = milligrams; n = number; NRT = nicotine replacement therapy; RCT = randomized controlled trial; SE = standard error.

Table 10. Adverse Event Results (KQ 3) of Pharmacotherapy Smoking Cessation Interventions Among Adults

Adverse event	Comparison	Number of RCTs	Number of Participants	IG Events	IG N	CG Events	CG N	Effect Estimate	95% CI	I^2
All CV adverse events[130]	NRT vs. placebo	21	11,647	202	6,329	83	5,318	RR: 1.81	1.35, 2.43	0%
Major CV adverse events[130]	NRT vs. placebo	21	11,647	12	6,329	7	5,318	RR: 1.38	0.58, 3.26	0%
Mortality[128]	NRT vs. placebo/ usual care	8	2,765	11	1,387	16	1,378	OR: 0.74	0.33, 1.67	0%
All CV adverse events[130]	Bupropion SR vs. placebo	27	10,402	50	5,947	42	4,455	RR: 1.03	0.71, 1.50	0%
Major CV adverse events[130]	Bupropion SR vs. placebo	27	10,402	15	5,947	25	4,455	RR: 0.57	0.31, 1.04	0%
Serious adverse events[121]	Bupropion SR vs. placebo/no bupropion SR control	33	9,631	114	5,328	80	4,303	RR: 1.30	1.00, 1.69	0%
All CV adverse events[130]	Varenicline vs. placebo	18	9,072	63	5,469	41	3,603	RR: 1.24	0.85, 1.81	0%
Major CV adverse events[130]	Varenicline vs. placebo	18	9,072	22	5,469	13	3,603	RR: 1.44	0.73, 2.83	0%
Major CV adverse events[135]	Varenicline vs. placebo	22*	9,232	34	5,431	18	3,801	RD: 0.27†	-0.10, 0.63	0%
Nonfatal serious adverse events[154]‡	Varenicline vs. placebo	17	7,725	126	4,274	76	3,451	RR: 1.36	1.03, 1.81	0%

* Most of the included trials included individuals with current (2 studies) or past (11 studies) cardiovascular disease

† For comparison, the risk ratio based on 14 trials with at least one event was 1.40 (95% CI, 0.82 to 2.39; I^2=0%; n=7,636)

‡ Medical occurrence that was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; or resulted in persistent or significant disability or incapacity. Does not distinguish between adverse events that can be attributed to and those unrelated to treatment and includes those occurring during the treatment and followup periods.

Abbreviations: CI = confidence interval; CG = control group; CV = cardiovascular; IG = intervention group; N = number; NRT = nicotine replacement therapy; OR = Odds ratio (based on DerSimonian-Laird random effects model); RCT = randomized controlled trial; RD = Risk difference; RR = Risk ratio; SR = sustained release; vs = versus.

Table 11. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Pregnant Women, by Alphabetical Order

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
*Chamberlain, 2013[110] Good	Behavioral counseling	Usual care; less intensive interventions; alternative interventions	Mar-13	86	WHO, Australian Government Department of Health and Aging, National Health Service (UK), EPPI-Center	RCTs, cluster-randomized trials, randomized cross-over trials, quasi-RCTs	Pregnant smokers or pregnant women who have recently quit smoking; women who are currently smoking or have recently quit and are seeking a pre-pregnancy consultation; or health professionals in trials of implementation strategies to support pregnant women to stop smoking	Smoking abstinence; perinatal outcomes	Not clearly stated	Any
*Coleman, 2012[92] Good	Pharm	Placebo; behavioral support or cognitive behavior therapy	Mar-12	6	British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council and the Department of Health, under the auspices of the UK Clinical Research Collaboration	RCTs	Pregnant smokers	Smoking abstinence; perinatal outcomes; AEs	NR	Any
Filion, 2011[116] Fair	Behavioral counseling	Usual care	June-10	8	Canadian Institutes of Health Research	RCTs	Pregnant smokers	Smoking abstinence	≥6 months	Any
Hettema, 2010[119] Fair	Motivational interviewing	Non-MI	June-08	Total: 31 (Pregnant: 8)	NR	RCTs	Pregnant and nonpregnant smoking adults	Smoking abstinence	Short-term (≤6 months) or long term (≥6 months); end of pregnancy	Any
Likis, 2014s[125] Good	Pharm or behavioral	Different intervention, usual care, placebo	Jan-13	59	AHRQ	RCTs or prospective cohorts (harms only)	Pregnant or postpartum who smoke or quit smoking during index pregnancy	Smoking abstinence; relapse; infant/child outcomes; AEs	Any	Clinician-initiated or intersects with clinical care

Table 11. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Pregnant Women, by Alphabetical Order

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Followup	Setting
Lumley, 2009[127] Good	Pharm or behavioral	Usual care	June-08	72	Australian Commonwealth Department of Health and Aging; 3 centres Collaboration (supported by the Victorian Department of Human Services)	RCTs and quasi-RCTs	Pregnant smokers in any care setting; women seeking a pre-pregnancy consultation; health professionals	Smoking abstinence; smoking reduction; maternal outcomes; infant outcomes; breastfeeding	Not clearly stated	Any
Myung, 2012[133] Good	Pharm	Placebo; no intervention; counseling	June-11	7	No funding was received	RCTs, quasi-RCTs, retrospective or prospective controlled studies	Pregnant smokers	Smoking abstinence; perinatal outcomes; AEs	Criterion not clearly stated, but range in the included studies was 12 to ~26 weeks	Any
Su, 2013[143] Fair	Behavioral, pharm, or incentive-based interventions	Not clearly stated, but placebo, routine care, counseling discussed	Dec-12	32	NR	RCTs, CCTs	Pregnant women smokers (focus on nonspontaneous quitters); interested in following women who quit during pregnancy through the postpartum period	Smoking abstinence	4 weeks after birth and up to 1 year postpartum to monitor the character-istics of relapse over time	Not clearly stated

*Review served as basis for main finding
†Quasi-RCTS are those that use quasi-random methods of assignment including alternation, date of birth, or medical record number.

Abbreviations: AE = adverse events; AHRQ = Agency for Healthcare Research and Quality; CCT = case-control trial; NR = not reported; Pharm = pharmacotherapy; RCT = randomized controlled trial; UK = United Kingdom; WHO = World Health Organization.

Table 12. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy and Safety of Tobacco Cessation Interventions Among Pregnant Women

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
Coleman, 2012[92]	6	Range: 30 to 1,050	Average age: NR Race: NR SES: NR Comorbidities/other substance use: NR	Smoking status: Range ≥1 to ≥15 (average cpd range) Nicotine dependence: NR consistently Partner smoking status: NR consistently Spontaneous quitting: NR consistently	Readiness to quit: 2 RCTs recruited participants who "agreed to set a quit date" or "who wanted to quit smoking" Quit history: NR consistently	All included RCTs evaluated NRT: -Placebo controlled (k=4) -NRT plus behavioral support with behavioral support alone (k=2)	Setting: NR Providers: NR, although 1 trial reported using "research midwives"
Chamberlain, 2013[110]	86	NR	Average age: most trials included women age >16 years, with only 2 trials targeting young women age <20 years and 1 trial including women age >15 years Race: 7 RCTs included mainly women belonging to an ethnic minority population: 2 were conducted in aboriginal communities and Alaskan native women; 1 RCT included >40% Maori women SES: 47 RCTs included women categorized as having low SES Comorbidities/other substance use: -RCTs targeted women with psychosocial risk factors (k=4) -RCTs conducted in women requiring methadone treatment	Smoking status: NR Nicotine dependence: NR consistently Partner smoking: Baseline NR; 4 studies examined associations with partner smoking and abstinence in late pregnancy Spontaneous quitting: NR consistently	Readiness to quit: NR consistently Quit history: 1,740 women reported "spontaneously quitting" when they became pregnant	Included 77 RCTs -Counseling (k=48) -Health education (k=7) -Feedback (k=7) -Incentives (k=4) -Social support (k=10) -Other (k=1) 1 RCT was aimed exclusively at women who had spontaneously quit smoking, and 11 trials included a relapse prevention component for women who had spontaneously quit. 13 of the counselling interventions involved telephone counselling and in 5 of these RCTs all counselling was provided via phone and 1 had only brief additional face to-face contact. 26 RCTs included self-help manuals as part of the intervention. 6 RCTs used video alone; 5	Setting: Most trials were conducted in public hospitals or community antenatal clinics Providers: In 26 RCTs the intervention was provided by routine pregnancy care providers; 43 trials used research project staff or automated technology

Table 12. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy and Safety of Tobacco Cessation Interventions Among Pregnant Women

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
			(k=2)			RCTs included computers; 1 RCT used audiotapes and 1 used text messages.	

Abbreviations: cpd = cigarettes per day; k = number of studies; NR = not reported; NRT = nicotine replacement therapy; pharm = pharmacotherapy; RCT = randomized controlled trial; SES = socioeconomic status.

Table 13. Descriptive Characteristics of Included Trials of Pharmacotherapy Interventions Among Pregnant Women

Review, Year	Study Design	N Randomized	Country	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Details	Outcomes of Interest
Berlin, 2014[101]	RCT	402	France	Average age: 29.3 years* Race: NR SES: Annual household income (Euro), % <12,000: 32.6† 12,000–30,000: 50.0† 30,000–100,000: 16.7† >100,000: 0.7† % Nulliparous: 27.9†	Smoking status: 10.5 (median cpd) Nicotine dependence: NR	Readiness to quit: Participants were required to have scored ≥5 on a motivational scale (range 0-10) Quit history: Previous quit attempts (≥1 week): 1*	Nicotine patch (10-15 mg/day) vs. placebo patch Participants were between 9 and 20 weeks pregnant and smoked ≥ 5 cpd.	Smoking abstinence, infant birth weight, head circumference, IUGR, serious adverse events
Coleman, 2012[184]	RCT	1,050	UK	Average age: 26.3 years† Race: % White: 97.0† SES: Mean age at leaving full-time education: 16.3 years† % Nulliparous: 0-1: 68.5	Smoking status: 14 (median cpd) † Nicotine dependence: NR	Readiness to quit: NR Quit history: NR	Behavioral counseling (1 face-to-face and 3 telephone sessions) plus nicotine patch (15 mg/16 hrs) vs. placebo patch plus behavioral counseling alone Participants were between 12 and 24 weeks pregnant and smoked ≥5 cpd.	Smoking abstinence; miscarriage; stillbirth; infant birth weight; preterm birth serious adverse events
Hotham 2006[187]	Non-placebo parallel-design RCT	40	Australia	Average age: 29.3 years† Race: NR SES: NR % Nulliparous: NR	Smoking status: 19.8† (average cpd) Nicotine dependence: NR	Readiness to quit: NR Quit history: NR	Behavioral counseling (5 min session at BL and <2 min sessions at followup visits) plus nicotine patch (15 mg/16 hrs for a maximum of 12 weeks) vs. behavioral counseling alone Participants were between 12 and 28 weeks pregnant and smoked ≥15 cpd.	Smoking abstinence; adverse reaction to patch

Table 13. Descriptive Characteristics of Included Trials of Pharmacotherapy Interventions Among Pregnant Women

Review, Year	Study Design	N Randomized	Country	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Details	Outcomes of Interest
Kapur 2001[186]	RCT	30	Canada	Average age: NR Race: NR SES: NA % Nulliparous: NR	Smoking status: NR Nicotine dependence: NR	Readiness to quit: participants required to "want to quit" upon entry Quit history: NR	Behavioral counseling (1 video followed by weekly telephone sessions) plus nicotine patch (15 mg/18 hrs for 8 wks; 10 mg/18 hrs for 2 wks; 5 mg/18 hrs for 2 wks) vs. placebo patch plus behavioral counseling alone Participants were between 12 and 24 weeks pregnant and smoked ≥15 cpd.	Smoking abstinence
Oncken 2008[188]	RCT	194	US	Average age: 25.1 years[†] Race, %: Hispanic: 54.1[†] Non-Hispanic white: 35.1[†] Non-Hispanic black: 7.7[†] Other: 3.1[†] SES, %: Less than HS: 50[†] HS: 33[†] More than HS: 17[†] % Nulliparous: 16.5[†]	Smoking status: 9.5 (average cpd) Nicotine dependence: NR	Readiness to quit: NR Quit history: Previous quit attempts, mean: 2.79	Behavioral counseling (8 face-to-face sessions) plus nicotine gum (2 mg) vs. placebo gum plus behavioral counseling alone Eligible participants were ≤26 weeks pregnant and smoked ≥1 cpd	Smoking abstinence; mean birth weight; gestational age; head circumference; neonatal length of stay
Pollak 2007[189]	Non-placebo parallel-design RCT	181	US	Average age: 27 years Race: % White: 69 % Black: 24 % Other: 8 SES, %: Less than HS: 28 HS/GED: 31 Vocational school: 7 Some college: 31 College graduate or higher: 5 % Nulliparous: 16	Smoking status: 11 (average cpd) Nicotine dependence: NR	Readiness to quit: Stage of readiness, %: Pre-contemplation: 1 Contemplation: 7 Preparation: 92 Quit history: Had a 24 hr quit attempt, %: 58	Behavioral counseling (5 face-to-face and 1 telephone session) plus the choice of NRT from patch (7-21 mg/16 hrs depending on cpd), gum (2 mg per each cpd), or lozenge (2 mg per each cpd) vs. behavioral counseling alone Participants were between 13 and 25 weeks pregnant and smoked ≥5 cpd.	Smoking abstinence; mean birth weight; serious adverse events

Table 13. Descriptive Characteristics of Included Trials of Pharmacotherapy Interventions Among Pregnant Women

Review, Year	Study Design	N Randomized	Country	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Details	Outcomes of Interest
Wisborg 2000[185]	RCT	250	Denmark	Average age: 28.4 years† Race: NR SES: Years of schooling: <10: 18.4† ≥10: 66.8† Missing: 14.8† % Nulliparous: 42.8†	Smoking status: 13.8† (average cpd) Nicotine dependence: NR	Readiness to quit: NR Quit history: Previous attempts to quit, % 0-2: 68.8† 3-15: 31.2†	Nicotine patch (15 mg/16 hrs for 8 weeks, 10 mg/16 hrs for 3 weeks) vs. placebo patch Participants were women who smoked ≥10 cigarettes after the first trimester.	Smoking abstinence; mean birth weight; preterm birth

*Median
†Calculated

Abbreviations: BL = baseline; cpd = cigarettes per day; GED = general education development; hrs = hours; HS = high school; IUGR = intrauterine growth restriction; N = number of participants; NR = not reported; NRT = nicotine replacement therapy; mg = milligrams; min = minutes; RCT = randomized controlled trial; SES = socioeconomic status; UK = United Kingdom; US = United States; vs = versus; yrs = years.

Table 14. Summary of Perinatal Health Outcome Results (KQ 1) of Behavioral Tobacco Cessation Interventions Among Pregnant Women Within Chamberlain Review[110]

Outcome	Intervention	Control	k	N	Abstinence measures*	Followup§	IG events	IG N	CG events	CG N	Risk Ratio‡ or mean difference	95% CI	I^2
Mean birthweight	All behavioral interventions‖	Usual care or control	19	9,859	21% PPA 68% BV	Late pregnancy, including during hospitalization for delivery	NA	4,948	NA	4,911	40.78	18.45, 63.10	0%
	Counseling	Usual care or control	12	5,392	17% PPA 67% BV	Late pregnancy, including during hospitalization for delivery	NA	2,619	NA	2,773	39.93	9.12, 70.74	0%
Low birth weight (<2500 g)	All behavioral interventions‖	Usual care or control	14	8,562	14% PPA 79% BV	Late pregnancy, including during hospitalization for delivery	304	4,298	381	4,264	0.82	0.71, 0.94	0%
	Counseling	Usual care or control	8	4,339	13% PPA 88% BV	Late pregnancy, including during hospitalization for delivery	151	2,090	200	2,249	0.83	0.68, 1.01	0%
Preterm birth (< 37 weeks)	All behavioral interventions‖	Usual care or control	14	7,852	29% PPA 79% BV	Late pregnancy, including during hospitalization for delivery	251	3,992	307	3,860	0.82	0.70, 0.96	0%
	Counseling	Usual care or control	8	3,447	25% PPA 89% BV	Late pregnancy, including during hospitalization for delivery	99	1,672	117	1,775	0.93	0.71, 1.20	0%
Stillbirth	All behavioral interventions‖	Usual care or control	7	5,414	0% PPA 57% BV	Late pregnancy, including during hospitalization for delivery	38	2,676	31	2,738	1.22	0.76, 1.95	0%
	Counseling	Usual care or control	5	2,454	0% PPA 80% BV	Late pregnancy, including during hospitalization for delivery	16	1,197	14	1,257	1.14	0.55, 2.33	0%

* Used point prevalence abstinence in late pregnancy for primary outcomes, and biochemically validated rates where available
† Weighted average quit rate
‡ Pooled risk ratios estimated using the Mantel-Haenszel random-effects model
§ Longest followup time point reported
‖ Behavioral interventions include counseling, health education, feedback, incentives, and social support

Abbreviations: BV = biochemically verified; CG = control group; CI = confidence interval; IG = intervention group; k = number of studies; N = number; NA = not applicable; PPA = point prevalence abstinence.

Table 15. Summary of Tobacco Abstinence Results (KQ 2) From Reviews of Tobacco Cessation Interventions Among Pregnant Women

Review, Year	Intervention	Control	k	N	Abstinence measures*	Followup‡	IG events	IG N	IG Quit Rate†	CG events	CG N	CG Quit Rate†	Risk Ratio§	95% CI	I^2
Coleman, 2012[92]	NRT, all forms‖	Placebo	4	1,520	25% CA 100% BV	Late pregnancy, including during hospitalization for delivery	93	762	12.2%	71	758	9.4%	1.27	0.95, 1.69	0%
Coleman, 2012[92] + study identified in bridge search	NRT, all forms¶	Placebo	5#	1,922	40% CA 100% BV	Late pregnancy, including during hospitalization for delivery	104	965	10.8%	81	957	8.5%	1.24	0.95, 1.64	0%
Chamberlain, 2013[110]	Any behavioral interventions**	Usual care or control	70	21,948	0% CA 79% BV	Late pregnancy, including during hospitalization for delivery	1,691	11,111	15.2%	1,213	10,837	11.2%	1.45	1.27, 1.64	60%
	Counseling	Usual care or control	45	17,681	0% CA 82% BV	Late pregnancy, including during hospitalization for delivery	1,283	8,830	14.5%	992	8,851	11.2%	1.37	1.17, 1.59	64%
	Social support	Usual care or control	10	1,683	0% CA 70% BV	Late pregnancy, including during hospitalization for delivery	168	845	19.9%	128	838	15.3%	1.29	0.97, 1.73	36%

* Used strictest available criteria to define abstinence (i.e., continuous, sustained, or prolonged abstinence was preferred over point prevalence abstinence and biochemically validated rates were used where available)
† Weighted average quit rate
‡ Longest followup time point reported
§ Pooled risk ratios estimated using the Mantel-Haenszel random-effects model
‖ 3/4 trials used nicotine patches
¶ 4/5 trials used nicotine patches
#Includes 4 trials identified in the Coleman review and one additional trial included from our bridge search
** Behavioral interventions include counseling, health education, feedback, incentives, and social support

Abbreviations: BV = biochemically verified; CA = continuous abstinence; CG = control group; CI = confidence interval; IG = intervention group; k = number of studies; N = number; NRT = nicotine replacement therapy.

Table 16. Inclusion Criteria of Included Existing Systematic Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults With Mental Health Disorders, by Alphabetical Order

Review, Year Quality	Intervention	Comparison	Last Search Date	Number of Included Studies	Funding Source	Study Design†	Population	Outcomes	Follow up	Setting
Banham, 2010[99]	Behavioral or pharm intervention designed to address smoking behavior and nicotine dependence, whether the aim was smoking cessation or reduction	Other interventions, placebo, or usual care	Jan-08	8	NR	RCTs	Adults with any form of severe and enduring mental ill health (severe mental illness was defined as any nonorganic disorder with psychotic features that results in a substantial disability, including schizophrenia, schizoaffective disorder, bipolar disorder or delusional disorder)	Smoking status; smoking reduction	NR	Inpatient or outpatient settings
Gierisch, 2010[117] Good	Antidepressants, NRT, brief smoking cessation counseling, behavioral counseling, or behavioral mood management treatment	Usual care or placebo	Mar-10	16	Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development	RCTs	Adult smokers with diagnosed depression	Smoking abstinence; AEs	≥3 months	Outpatient (e.g., mental health clinics, primary care) or delivered through remote communication technologies (e.g., telephone, Web)
*Tsoi, 2013[146] Good	Pharm or behavioral	Another intervention, placebo or usual care	Oct-12	34	NHS National Institute for Health Research	RCTs or quasi-	Adult smokers with schizophrenia or schizoaffective disorder	Smoking abstinence; changes in mental state	≥6 months	Inpatient units, the community, or outpatient psychiatric treatment sites
*van der Meer, 2013[149] Good	Pharm or psychosocial intervention, or combination	Usual care or placebo	April-13	49	NR	RCTs	Adult smokers with current or past depression	Smoking abstinence	≥6 months	Any

*Review served as basis for main finding

†Quasi-RCTS are those that use quasi-random methods of assignment including alternation, date of birth, or medical record number.

Abbreviations: AE = adverse event; NHS = National Health Service; NR = not reported; pharm = pharmacotherapy; RCT = randomized controlled trial.

Table 17. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy and Safety of Tobacco Cessation Interventions Among Adults With Mental Health Disorders

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
van der Meer, 2013[149]	49	14 to 5,046	Average age (range): 24 to 57 Sex (% female): 7.8 to 100 Race: NR SES: NR Comorbidities/other substance abuse: Patients with substance abuse disorders were generally excluded from the studies in this review, with the exception of 1 study conducted at substance abuse treatment sites	Smoking status: 7.9 to 32.3 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: NR consistently Quit history: NR consistently	49 RCTs included -Investigating smoking cessation interventions with specific mood management components for handling depression (k=33) -Investigating antidepressants vs placebo (k=16)	Setting: Trials conducted in community, university, and clinical settings including hospitals Providers: NR
Tsoi, 2013[146]	34	9 to 298	Average age (range): 34 to 49 Sex (% female): NR; "predominantly male" Race: NR consistently SES: NR Comorbidities/other substance use: Although the *review* did not exclude patients with schizophrenia or schizoaffective disorder who had other substance misuse disorder or additional psychiatric disorders, a significant number of the *included studies* explicitly excluded participants with any active substance misuse other than nicotine.	Smoking status: 7 to 41 (average cpd range) Nicotine dependence: NR consistently	Readiness to quit: 16 RCTs stated that participants had expressed interest in quitting or reducing smoking Quit history: NR consistently	34 RCTs included -Interventions focused on smoking cessation, reduction, or relapse prevention (k=26) -Had a primary aim other than the one above (k=8) There was a range of interventions. Of the studies comparing pharmacotherapy with placebo, the most common interventions were bupropion SR (k=8), nicotine patch (k=3) and varenicline (k=2). 2 RCTs compared the combination of bupropion SR and patch, with patch and placebo; 2 RCTs compared the efficacy of different dosages of patch for smoking cessation. Some of the drug therapy studies provided psychosocial interventions to all participants. These psychosocial interventions	Setting: "Most trials recruited participants from the community." Providers: NR

Table 17. Descriptive Characteristics of Included Studies Within the Main Reviews on the Efficacy and Safety of Tobacco Cessation Interventions Among Adults With Mental Health Disorders

Review, Year	Number of Included Studies	Sample Size (Range)	Demographic Characteristics	Baseline Smoking Status	Readiness to Quit/ Quit History	Intervention Characteristics	Treatment Setting/ Provider Characteristics
						included group cognitive behavioral therapy k=4), group therapy for motivational enhancement, psychoeducation and relapse prevention (k=1); group behavioral therapy (k=2); smoking cessation educational classes along with discussions with health educators (k=1); group psychoeducation (k=1); group therapy using the ACS Fresh Start Program (k=1) and individual smoking cessation counseling (k=2). The duration of drug treatment varied from 7 hours to 6 months. 5 RCTs predominantly examined the effect of behavioral interventions ranging from a single session of motivational interviewing to specialized group therapy of various designs. 1 RCT used repetitive transcranial magnetic stimulation to investigate whether this was effective for smoking cessation. 3 RCTs investigated the combined effect of pharmacological and psychosocial interventions.	

Abbreviations: ACS = American Cancer Society; cpd = cigarettes per day; k = number of studies; NR = not reported; RCT = randomized controlled trial; SES = socioeconomic status; SR = sustained release; vs = versus.

Table 18. Summary of Evidence for the General Adult Population

Key Question	Intervention	Number of included reviews	Summary of findings	Consistency	Major limitations	Applicability
1: Health outcomes	Pharm	0	NA	NA	NA	NA
	Combined pharm and behavioral	0	NA	NA	NA	NA
	Behavioral	1	One trial found favorable effects on all-cause and coronary disease mortality and lung cancer incidence and mortality 20 yrs following an intensive behavioral intervention, although results were not statistically significant.	NA	Only 1 review reported the results of 1 intervention in men on health outcomes. Within that trial, the rate of smoking in control group participants declined steadily over the followup period, narrowing the intervention effect.	One trial conducted among civil servant men aged 40-59 yrs in the UK with high risk of cardiorespiratory disease. Intervention took place in the 1970's.
	ENDS	0 RCTs	NA	NA	NA	NA
2: Cessation outcomes	Pharm	6	NRT, bupropion SR, and varenicline improve the chances of quitting smoking. Reviews suggested that NRT might increase smoking abstinence at 6 months or longer by 53-68%; bupropion SR by 49-76%; and varenicline by 102-155%. Absolute quit differences averaged 7% for NRT; 8.2% for bupropion SR, and 26% for varenicline. No significant differences between different NRT products and relative rates of abstinence were similar across settings. Using a combination of NRT products increases quitting more than the use of a single NRT product. In general, there were no significant differences between different classes of medications in direct comparisons.	Consistent	Possibility of publication bias but unlikely that the presence of additional studies with lower relative risks would alter the findings given large number of studies and consistency in findings. Trials with pharmaceutical funding have been shown to have slightly higher effect sizes than nonindustry funded studies; given the number of included trials funded by pharmaceutical companies (particularly for varenicline) the magnitude of the effects may be smaller than estimates suggest.	Most of the included studies within each review were conducted in North America and should be applicable to the US health system. Treatment effects appear to be comparable in a range of populations, settings and types of interventions and in smokers with and without other co-morbidities. The literature almost exclusively addressed treatment for cigarette smoking, as opposed to the use of other forms of tobacco, so results may not be generalizable to all forms of tobacco.
	Combined pharm and behavioral	1	Combined pharmacotherapy and behavioral interventions increase quit rates by 70-100% compared with no or minimal treatment.	Consistent	May be risk of bias due to lack of blinding of participants.	

Table 18. Summary of Evidence for the General Adult Population

Key Question	Intervention	Number of included reviews	Summary of findings	Consistency	Major limitations	Applicability
	Behavioral	26	Health provider advice and counseling, tailored self-help materials, and telephone counseling showed modest but significant increased smoking cessation at 6 or more months relative to controls (18% to 96%). Providing more intense adjunctive behavioral support to smokers receiving pharmacotherapy may increase cessation by 9-24%. Evidence on the use of mobile phone support, internet-based interventions, and complementary and alternative therapies was limited and not definitive.	Consistent	Individual trials may be represented in more than one review and/or meta-analysis. Several of the meta-analyses treated comparisons between different trial arms as separate studies and were not consistent in their reporting or handling of multiple comparisons. Fixed-effects models were used in nearly all meta-analyses.	
	ENDS	2 RCTs	One trial found no statistically significant difference in biochemically verified abstinence at 6 months between those receiving e-cigs vs nicotine patch or placebo e-cig (n=657). The other trial (n=300) found a borderline statistically significant higher quit rate among those receiving nicotine-containing e-cigs (11%) vs no nicotine e-cigs (4%) at 12 months.	Consistent	Insufficient statistical power to detect differences and differential high loss to followup in both trials (22-40%)	Two trials took place in New Zealand and Italy. Both trials used older models of e-cigs, one of which is no longer available. One trial conducted among smokers not wanting to quit.
3: Adverse events	Pharm	8	NRT, bupropion SR, and varenicline are not associated with an increased risk in major CV adverse events. NRT is associated with a higher rate of any CV adverse events largely driven by low-risk events, typically tachycardia. There was a marginal, nonsignificant increase in serious AEs in those taking bupropion SR, but no difference for serious psychiatric AEs. The evidence for the safety of varenicline is still under investigation; one review suggested a 36% increased risk of nonfatal serious AEs among those taking varenicline versus control.	Consistent	Many trials that report cessation effectiveness do no report AEs, particularly CV- or neuropsychiatric-specific AEs. AEs typically measured through passive reporting and therefore susceptible to underreporting.	Likely applicable across settings and populations.

Table 18. Summary of Evidence for the General Adult Population

Key Question	Intervention	Number of included reviews	Summary of findings	Consistency	Major limitations	Applicability
	Combined pharm and behavioral	0	NA	NA	NA	NA
	Behavioral	2	Minor AEs related to ear-acupuncture, ear-acupressure and other auricolutherapy have been reported. AEs related to other behavioral or complementary and alternative therapies have not been documented.	NA	Only 2 reviews assessed AEs related to behavioral interventions; one found no studies that reported AEs.	Limited evidence on harms limits applicability.
	ENDS	2 RCTs	Two RCTs reported no serious AEs in either the intervention or control groups related to product use and no difference in the frequency of AEs among study groups. One trial found a higher proportion of serious AEs among the e-cig group vs. the NRT patch group (19.7% vs 11.8%).	Consistent	Insufficient statistical power to detect differences and differential high loss to followup in both trials (22-40%) One study did not report methods for AEs reporting.	Two trials took place in New Zealand and Italy. Both trials used older models of e-cigs, one of which is no longer available.

Abbreviations: ENDS = electronic nicotine delivery system; NA = not applicable; NRT = nicotine replacement therapy; pharm = pharmacotherapy; RCT = randomized controlled trial; SR = sustained release; UK = United Kingdom; US = United States; yrs = years.

Table 19. Summary of Evidence for Pregnant Women

Key Question	Intervention	Number of included reviews	Summary of findings	Consistency	Major limitations	Applicability
1: Health outcomes	Pharm	4	Limited evidence of NRT on perinatal and child health benefits. Three out of four NRT trials reported fewer preterm births in the intervention group, but only one was statistically less than placebo. Two trials reported higher birth weightin the NRT group; two larger trials found no difference. Followup data from the largest NRT trial found higher rate of 'survival with no impairment' at 2 years among children of women assigned to NRT intervention vs placebo (73% vs 65%). No trials of bupropion SR or varenicline among pregnant women.	NA	Rare health outcomes and few trials of NRT limited statistical precision and ability to draw conclusions based on the current evidence. Limited information on the women approached for participation that declined, and low participation rates.	Trials mainly conducted in high-income countries including the US, relevant and applicable. Pharmacotherapy trials were placebo controlled and outcomes based on well-established measures used in routine health care settings, likely applicable results. Given stigma of smoking during pregnancy, challenging to recruit pregnant smokers. Those who disclose smoking status and willing to participate in trials may differ from general population (e.g., motivation to quit).
	Behavioral	3	Statistically significant benefit of behavioral interventions on mean birthweight, low birthweight, and preterm birth vs usual care or control.	Consistent		
2: Cessation outcomes	Pharm	5	No statistical evidence of NRT efficacy for validated smoking cessation in late pregnancy, but limited power, and all trials in the direction of benefit (pooled analysis based on 5 placebo-controlled trials). No trials of bupropion SR or varenicline among pregnant women.	Consistent	Limited information on the women approached for participation that declined, and low participation rates.	
	Behavioral	6	Pooled estimates of a range of behavioral interventions from 70 studies suggested benefits for validated smoking cessation, with a similar benefit when limited to the most common intervention (counseling). Heterogeneity was moderate for the pooled effect, but there was no evidence of subgroup effects by intervention type, number of intervention components, or outcome ascertainment approach.	Consistent		

Table 19. Summary of Evidence for Pregnant Women

Key Question	Intervention	Number of included reviews	Summary of findings	Consistency	Major limitations	Applicability
3: Adverse events	Pharm	5	No evidence of perinatal harms from NRT. One trial found a higher rate of cesarean section for women assigned to NRT; followup from the same trial was reassuring for child health outcomes. No trials of bupropion SR or varenicline among pregnant women.	NA	Few trials of NRT and not all reported consistently on health outcomes and adverse events.	
	Behavioral	1	No serious adverse events reported.	NA	Inconsistent data collection across trials; most reliant on passive reporting.	
	Behavioral	1	No serious adverse events reported.	NA	Inconsistent data collection across trials; most reliant on passive reporting.	

Abbreviations:; NA = not applicable; NRT = nicotine replacement therapy; pharm = pharmacotherapy; SR = sustained release; US = United States; vs = versus**.**

Table 20. Summary of Evidence for Individuals With Mental Health Conditions

Key Question	Intervention	Number of included reviews	Summary of findings	Consistency	Major limitations	Applicability
1: Health outcomes	Pharm and/or behavioral	2	No evidence on health outcomes related to cessation interventions among individuals with depression. Among individuals with schizophrenia, no evidence that bupropion SR worsened mental health outcomes (8 studies).	NA Consistent (bupropion SR)	Some trials were subgroup analyses with post hoc determination of mental health status.	Trials were not all conducted in primary care settings; some were inpatient (especially for schizophrenia/affective disorder).
2: Cessation outcomes	Pharm and/or behavioral	4	Too few trials available to draw conclusions from pooled analysis on pharmacological intervention for smokers with depression. Evidence of benefit of bupropion SR among people with schizophrenia however, results based on few events and participants in the 5 available trials (n=214). Evidence that addition of a mood management intervention to standard smoking cessation interventions was beneficial for people with current or past depression. Limited evidence of behavioral interventions among schizophrenics.	NA Consistent NA	Some trials were subgroup analyses with post hoc determination of mental health status. Few studies, participants, and events, and heterogeneous interventions, limit statistical inference.	Trials were not all conducted in primary care settings; some were inpatient (especially for schizophrenia/affective disorder).
3: Adverse events	Pharm and/or behavioral	3	Limited data available on serious AEs related to cessation interventions among individuals with depression or schizophrenia. Few trials suggested no severe, life-threatening AEs related to pharmacotherapies.	NA	Only 3 studies of pharmacotherapy treatment among individuals with depression reported detailed data on AEs.	Limited evidence on harms limits applicability.

Abbreviations: AE = adverse events; CV = cardiovascular; e-cig = electronic cigarette; ENDS = electronic nicotine delivery system; n = number of participants; NA = not applicable; NRT = nicotine replacement therapy; pharm = pharmacotherapy; RCT = randomized controlled trial; SR = sustained release.

Appendix A. 2009 USPSTF Clinical Summary: Counseling and Interventions to Prevent Tobacco Use and Tobacco-Caused Disease in Adults and Pregnant Women

Population	Adults Age ≥18 Years	Pregnant Women of Any Age
Recommendation	**Ask about tobacco use. Provide tobacco cessation interventions to those who use tobacco products.**	**Ask about tobacco use. Provide augmented pregnancy-tailored counseling for women who smoke.**
	Grade: A	**Grade: A**
Counseling	The "5-A" framework provides a useful counseling strategy: 1. **A**sk about tobacco use. 2. **A**dvise to quit through clear personalized messages. 3. **A**ssess willingness to quit. 4. **A**ssist to quit. 5. **A**rrange follow-up and support. Intensity of counseling matters: brief one-time counseling works; however, longer sessions or multiple sessions are more effective. Telephone counseling "quit lines" also improve cessation rates.	
Pharmacotherapy	Combination therapy with counseling and medications is more effective than either component alone. FDA-approved pharmacotherapy includes nicotine replacement therapy, sustained-release bupropion, and varenicline.	The USPSTF found inadequate evidence to evaluate the safety or efficacy of pharmacotherapy during pregnancy.
Implementation	Successful implementation strategies for primary care practice include: • Instituting a tobacco user identification system. • Promoting clinician intervention through education, resources, and feedback. • Dedicating staff to provide treatment, and assessing the delivery of treatment in staff performance evaluations.	
Relevant Recommendations from the USPSTF	Recommendations on other behavioral counseling topics are available at http://www.uspreventiveservicestaskforce.org.	

Abbreviations: FDA = U.S. Food and Drug Administration; USPSTF = U.S. Preventive Services Task Force.

Search Strategies

Systematic Evidence Review Search

Database: **AHRQ**

Treating Tobacco Use and Dependence: 2009 Update
http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html

Smoking Cessation Interventions During Pregnancy and the Postpartum Period [Research Protocol – Mar 8, 2013]
http://effectivehealthcare.ahrq.gov/ehc/products/517/1423/Pregnancy-Smoking%20Cessation-130311.pdf

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

Pharmacologic-based Strategies for Smoking Cessation – September 2010
http://www.cadth.ca/en/products/health-technology-assessment/publication/3141

Database: **Cochrane Database of Systematic Reviews** (**Issue 12 of 12, Dec 2012)**

#1 tobacco:ti from 2009 to 2013, in Cochrane Reviews (Reviews only)
#2 smoking:ti from 2009 to 2013, in Cochrane Reviews (Reviews only)
#3 smoker*:ti from 2009 to 2013, in Cochrane Reviews (Reviews only)
#4 nicotine:ti from 2009 to 2013, in Cochrane Reviews (Reviews only)
#5 cigarette*:ti from 2009 to 2013, in Cochrane Reviews (Reviews only)
#6 #1 or #2 or #3 or #4 or #5

Database: **Community Guide**

Reducing tobacco use and secondhand exposure [multiple TF recommendations]
http://www.thecommunityguide.org/tobacco/index.html

Database: **Database of Abstracts of Reviews of Effects (Via CRD)**

(smoking):TI OR (smoker*):TI OR (tobacco):TI OR (nicotine):TI OR (cigarette*):TI IN DARE FROM 2009 TO 2013

Database: **Health Technology Assessment**

(smoking):TI OR (smoker*):TI OR (tobacco):TI OR (nicotine):TI OR (cigarette*):TI IN HTA FROM 2009 TO 2013

Database: **Institute of Medicine**

Combating Tobacco in Military and Veteran Populations, June 2009
http://www.iom.edu/Reports/2009/MilitarySmokingCessation.aspx

Ending the Tobacco Problem: A Blueprint for the Nation, May 2007
http://www.iom.edu/Reports/2007/Ending-the-Tobacco-Problem-A-Blueprint-for-the-Nation.aspx

Database: **NHS HTA Programme**

Relapse prevention in UK Stop Smoking Services: current practice, systematic reviews of effectiveness and cost-effectiveness analysis - October 2010
http://www.journalslibrary.nihr.ac.uk/hta/volume-14/issue-49

Cytisine for smoking cessation
Protocol October 2012
http://www.hta.ac.uk/protocols/201200460001.pdf

Effectiveness and cost-effectiveness of computer and other electronic aids for smoking cessation: a systematic review and network meta-analysis - October 2012
http://www.journalslibrary.nihr.ac.uk/hta/volume-16/issue-38

Evaluating longer term outcomes of NHS stop smoking services
Protocol December 2012
http://www.hta.ac.uk/protocols/200901610001.pdf

Database: **NICE**

Quitting smoking in pregnancy and following childbirth
June 2010, expected update July 2013
http://guidance.nice.org.uk/PH26

Smokeless tobacco cessation - South Asian communities
September 2012, expected update September 2015
http://guidance.nice.org.uk/PH39

Tobacco harm reduction
June 2013, expected update June 2016
http://guidance.nice.org.uk/PH45

Smoking cessation - acute, maternity and mental health services
Anticipated publication date: November 2013
http://guidance.nice.org.uk/PHG/51

Database: **PubMed**
---
1) "Smoking Cessation"[Mesh] OR "Tobacco Use Cessation"[Mesh:NoExp] OR "Tobacco Use Disorder"[Mesh] OR "Smoking/prevention and control"[Mesh:NoExp]
2) #1 AND systematic[sb] Limits: English, Adult: 19+ years, Publication Date from 2008 to 2013
3) (smoking[ti] OR smoker*[ti] OR tobacco[ti] OR nicotine[ti] OR cigarette*[ti])
4) #3 AND systematic[sb]
5) #4 AND (in process[sb] OR publisher[sb] OR pubmednotmedline[sb]) Limits: English, Publication Date from 2009 to 2013
6) #2 OR #5

Database: **PsycINFO** <1806 to July Week 5 2013 >
---
1 tobacco smoking/
2 smoking cessation/
3 Smokeless tobacco/
4 (smoking or smoker$ or tobacco or nicotine or cigarette$).ti.
5 1 or 2 or 3 or 4
6 limit 5 to "300 adulthood <age 18 yrs and older>"
7 limit 6 to ("0830 systematic review" or 1200 meta analysis)
8 limit 7 to (english language and yr="2009 -Current")

Pregnant Women Evidence Search

Database: **CENTRAL** <Issue 7 of 12, July 2014>

#1 (pregnan* or prenatal or "pre natal" or perinatal or "peri natal" or antenatal or "ante natal" or antepartum or "ante partum" or postnatal or "post natal" or postpartum or "post partum" or puerperal):ti,ab,kw 28995
#2 (smoking or smoker* or tobacco or nicotine or cigarette*):ti,ab,kw 16591
#3 nicotine:ti,ab,kw next replacement:ti,ab,kw next therap*:ti,ab,kw 542
#4 nicotine:ti,ab,kw near/3 (patch* or gum* or spray* or lozenge*):ti,ab,kw 1155
#5 (Bupropion or Zyban or Varenicline or Chantix or Champix):ti,ab,kw 1182
#6 (drug* or pharm*):ti 15323
#7 #3 or #4 or #5 or #6 17791
#8 #1 and #2 and #7 Publication Year from 2012 to 2014, in Trials 11

Database: **Medline**
Ovid MEDLINE(R) without Revisions <1996 to August Week 1 2014>
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 14, 2014>
Ovid MEDLINE(R) Daily Update <August 14, 2014>
---
1 Pregnancy/ (306774)
2 Pregnant women/ (2284)
3 Prenatal care/ (11476)

4 Perinatal care/ (2682)
5 Postnatal care/ (2484)
6 Postpartum period/ (8090)
7 Peripartum period/ (333)
8 Maternal Health Services/ (5284)
9 Pregnancy complications/ (31416)
10 Puerperal Disorders/ (3628)
11 pregnan$.ti,ab. (210464)
12 prenatal.ti,ab. (43895)
13 pre natal.ti,ab. (528)
14 perinatal.ti,ab. (32454)
15 peri natal.ti,ab. (103)
16 antenatal.ti,ab. (16549)
17 ante natal.ti,ab. (237)
18 antepartum.ti,ab. (2505)
19 ante partum.ti,ab. (219)
20 postnatal.ti,ab. (52436)
21 post natal.ti,ab. (3484)
22 postpartum.ti,ab. (23067)
23 post partum.ti,ab. (4670)
24 new mother$.ti,ab. (825)
25 puerperal.ti,ab. (1782)
26 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (429666)
27 "Tobacco Use Disorder"/ (6738)
28 Smoking/ (73210)
29 "Tobacco Use Cessation"/ (723)
30 Smoking Cessation/ (17952)
31 smoking.ti,ab. (114959)
32 smoker$.ti,ab. (45894)
33 tobacco.ti,ab. (52031)
34 nicotine.ti,ab. (20548)
35 cigarette$.ti,ab. (33842)
36 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (188107)
37 "Tobacco Use Cessation Products"/ (603)
38 Nicotinic Agonists/ (5531)
39 Bupropion/ (2050)
40 Benzazepines/ (4838)
41 Quinoxalines/ (5408)
42 nicotine replacement therap$.ti,ab. (1739)
43 (nicotine adj3 (patch$ or gum$ or nasal spray$ or lozenge$)).ti,ab. (1502)
44 Bupropion.ti,ab. (2638)
45 Zyban.ti,ab. (115)
46 Varenicline.ti,ab. (899)
47 Chantix.ti,ab. (45)
48 Champix.ti,ab. (33)

49 (drug$ or pharm$).ti. (261302)
50 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (279019)
51 26 and 36 and 50 (725)
52 "Tobacco Use Disorder"/dt [Drug Therapy] (736)
53 26 and 52 (27)
54 51 or 53 (730)
55 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ (177894)
56 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (502141)
57 Random$.ti,ab. (583977)
58 control groups/ or double-blind method/ or single-blind method/ (97302)
59 clinical trial$.ti,ab. (180675)
60 controlled trial$.ti,ab. (106233)
61 meta analy$.ti,ab. (60992)
62 55 or 56 or 57 or 58 or 59 or 60 or 61 (1070505)
63 54 and 62 (89)
64 limit 63 to (english language and yr="2012 -Current") (22)

Database: ***PsycINFO <1806 to August Week 2 2014>***
---
1 Pregnancy/ (15766)
2 Expectant Mothers/ (532)
3 Prenatal Care/ (1297)
4 Perinatal Period/ (1743)
5 Postnatal Period/ (3654)
6 pregnan$.ti,ab,id. (33146)
7 prenatal.ti,ab,id. (13783)
8 pre natal.ti,ab,id. (181)
9 perinatal.ti,ab,id. (6862)
10 peri natal.ti,ab,id. (55)
11 antenatal.ti,ab,id. (2103)
12 ante natal.ti,ab,id. (40)
13 antepartum.ti,ab,id. (203)
14 ante partum.ti,ab,id. (9)
15 postnatal.ti,ab,id. (13564)
16 post natal.ti,ab,id. (717)
17 postpartum.ti,ab,id. (7864)
18 post partum.ti,ab,id. (818)
19 puerperal.ti,ab,id. (431)
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (60200)
21 tobacco smoking/ (22978)
22 smoking cessation/ (9199)
23 Smokeless tobacco/ (562)
24 (smoking or smoker$ or tobacco or nicotine or cigarette$).ti,ab,id. (48166)

25 21 or 22 or 23 or 24 (48286)
26 Drug Therapy/ (108330)
27 Bupropion/ (792)
28 nicotine replacement therap$.ti,ab,id. (915)
29 (nicotine adj3 (patch$ or gum$ or nasal spray$ or lozenge$)).ti,ab,id. (1104)
30 Bupropion.ti,ab,id. (1686)
31 Zyban.ti,ab,id. (43)
32 Varenicline.ti,ab,id. (421)
33 Chantix.ti,ab,id. (27)
34 Champix.ti,ab,id. (13)
35 (drug$ or pharm$).ti. (51426)
36 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (147347)
37 20 and 25 and 36 (240)
38 random$.ti,ab,id,hw. (132759)
39 placebo$.ti,ab,hw,id. (31321)
40 controlled trial$.ti,ab,id,hw. (21428)
41 clinical trial$.ti,ab,id,hw. (24164)
42 meta analy$.ti,ab,hw,id. (19063)
43 treatment outcome clinical trial.md. (27525)
44 38 or 39 or 40 or 41 or 42 or 43 (187717)
45 37 and 44 (39)
46 limit 45 to (english language and yr="2012 -Current") (13)

Database: ***PubMed, publisher-supplied records***

Search	Query	Items found
#12	Search **#11 AND publisher[sb] AND English[Language] AND ("2012"[Date - Publication] : "2014"[Date - Publication])**	8
#11	Search **#4 AND #5 AND #10**	495
#10	Search **#6 OR #7 OR #8 OR #9**	314642
#9	Search **drug*[ti] OR pharm*[ti]**	307939
#8	Search **Bupropion[tiab] OR Zyban[tiab] OR Varenicline[tiab] OR Chantix[tiab] OR Champix[tiab]**	3743
#7	Search **nicotine[tiab] AND (patch*[tiab] OR gum*[tiab] OR spray*[tiab] OR lozenge*[tiab])**	2699
#6	Search **nicotine replacement therap*[tiab]**	1812
#5	Search **smoking[tiab] OR smoker*[tiab] OR tobacco[tiab] OR nicotine[tiab] OR cigarette*[tiab]**	237785
#4	Search **pregnan*[tiab] OR prenatal[tiab] OR "pre natal"[tiab] OR perinatal[tiab] OR "peri natal"[tiab] OR antenatal[tiab] OR "ante natal"[tiab] OR antepartum[tiab] OR "ante partum"[tiab] OR postnatal[tiab] OR "post natal"[tiab] OR postpartum[tiab] OR "post partum"[tiab] OR puerperal[tiab]**	543639

Electronic Nicotine Delivery Systems Evidence Search

Database: **PubMed Strategy 3.1.2015**

Search (((e-cigarette*[Title/Abstract]) OR electronic cigarette*[Title/Abstract]) OR electric nicotine delivery[Title/Abstract]) OR electronic nicotine delivery[Title/Abstract] Filters: Publication date from 2008/01/01 to 2015/12/31; English

Database: **Cochrane Database of Systematic Reviews : Issue 5 of 12, May 2014**

ID	Search
#1	electronic next cigarette*:ti,ab,kw
#2	e next cigarette*:ti,ab,kw
#3	electronic next nicotine next delivery:ti,ab,kw
#4	#1 or #2 or #3 Publication Date from 2008 to 2014, in Trials
#5	#1 or #2 or #3 in Cochrane Reviews (Reviews and Protocols)

Database: **Scopus 5-13-2014**

TITLE-ABS-KEY("e-cigarette*" OR "electronic cigarette*" or "electronic nicotine delivery") AND (LIMIT-TO(PUBYEAR,2014) OR LIMIT-TO(PUBYEAR,2013) OR LIMIT-TO(PUBYEAR,2012) OR LIMIT-TO(PUBYEAR,2011) OR LIMIT-TO(PUBYEAR,2010) OR LIMIT-TO(PUBYEAR,2009) OR LIMIT-TO(PUBYEAR,2008)) AND (LIMIT-TO(LANGUAGE,"English"))

Appendix B Table 1. Inclusion and Exclusion Criteria

Category	Include	Exclude
Study design	Systematic reviews, including review-of-reviews, with or without meta-analysis A review will be considered "systematic" if it: 1) includes a clear statement of the purpose of the review; 2) describes the search strategy; 3) indicates the criteria used to select studies for inclusion; and 4) presents the findings relevant to the main purpose of the review, including those that did not favor the intervention. Systematic reviews that include experimental and/or observational study designs will be included	
Aim	Tobacco cessation in current tobacco users, regardless of readiness to quit	• Primary prevention of tobacco use • Tobacco harm–reduction strategies • Relapse prevention interventions
Condition	Current use of any tobacco product, including, but not limited to: cigarettes, pipes, cigars, cigarillos, little cigars, bidis, kreteks, tobacco (including chew, snuff [including snus], and dissolvable tobacco in the form of strips, sticks, or lozenges), or smoking tobacco through a hookah or waterpipe	
Population	Adults (age ≥18 years), including pregnant women and individuals with mental health conditions, who are current smokers Includes reviews that focus on specific primary care–relevant subgroups (e.g., young adults; older adults; specific racial/ethnic groups; lesbian, gay, bisexual, and transgender individuals; veterans; low-income; low education; substance users)	Reviews in which >50% of the included studies focus on: • Children and adolescents • Partners • Providers • Psychiatric inpatients • Other nonmental health comorbid conditions (e.g., chronic obstructive pulmonary disease, cardiovascular conditions, cancer, HIV)
Interventions	Primary care–relevant tobacco cessation interventions, including behavioral interventions and/or pharmacotherapy, with or without referral Examples include: • Advice and counseling (including technology- and web-based services) • Self-help materials (including technology and web-based services) • Referral to quitlines • Complementary and alternative therapies (e.g., acupuncture, hypnosis) • Exercise interventions • Nicotine replacement therapy (gum, inhaler, lozenge, nasal spray, patch) • Bupropion (Zyban®) • Varenicline tartrate (Chantix®) • Electronic nicotine delivery systems (ENDS) or electronic cigarettes*	• System-level interventions • Broad public health initiatives (e.g., mass media, community-wide) • Medications that are not approved by the U.S. Food and Drug Administration as first-line tobacco cessation agents (e.g., clonidine, nortriptyline, selective serotonin reuptake inhibitors, anxiolytics, benzodiazepines, beta-blockers, opioid antagonists/naltrexone)
Setting	Any setting applicable to primary care	Reviews limited to studies that take place in worksites, specialty care, or other settings not applicable to primary care
Comparators	• No intervention • Usual care • Waitlist • Attention control (e.g., similar in format and intensity, but intervention on a different content area) • Minimal intervention (no more than a single brief contact [i.e., <5 minutes] per year or brief written materials, such as pamphlets)	

Appendix B Table 1. Inclusion and Exclusion Criteria

Category	Include	Exclude
	• Active intervention (i.e., more than a single brief contact per year or brief written materials)	
Outcome assessment	Based on self-report or biochemically validated reports (e.g., expired carbon monoxide; cotinine measured in saliva, urine, or blood; cotinine–creatinine ratio; thiocyanate)	Population-based smoking rates (i.e., not based on study sample, but on underlying population)
Outcomes	**KQ 1: Health and other outcomes** *Health outcomes:* • All-cause mortality • Tobacco-related mortality • Tobacco-related morbidity (including, but not limited to: cancer, asthma, cardiovascular disease, chronic bronchitis, or other respiratory disorders) • Perinatal morbidity/mortality • Dental/oral health • Quality of life as measured by validated scales *Other outcomes:* ▪ Health care utilization **KQ 2: Behavioral outcomes** ▪ Tobacco cessation/tobacco abstinence (continuous abstinence or point prevalence abstinence) **KQ 3: Adverse events** ▪ Serious treatment-related harms at any time point after the intervention began ▪ Weight gain ▪ Emotional distress (e.g., worsening of symptoms such as depression, anxiety, psychosis; loss of associates or friends) ▪ Adverse events associated with medications ▪ Paradoxical increase in tobacco use ▪ Demoralization due to failed quit attempt ▪	Reviews that only report: • Smoking/tobacco reduction (based on frequency/quantity only) • Reduction in withdrawal symptoms • Attitudes, knowledge, or beliefs related to tobacco use • Intentions to change behavior • Intervention participation/compliance
Outcome assessment timing	**KQs 1, 2:** ≥6-month followup after quit date/start of intervention **KQ 3:** Harms reported at any point after quit date	<6-month followup after quit date/start of intervention
Study geography	Reviews that do not exclusively take place in nondeveloped countries (http://hdr.undp.org/en/statistics) Developed countries: Andorra, Argentina, Australia, Austria, Barbados, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Seychelles, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States	Reviews in which >50% of included studies take place in countries with a Human Development Index below "Very High"
Publication language	English	Any language other than English
Publication date	2009 to present	Reviews published before 2009
Quality rating	Fair or good	Poor

* The review of ENDS or e-cigarette evidence did not adopt the review-of-review approach given the emerging nature of the technology. The specific criteria for inclusion and exclusion of these studies are outlined in narrative form.

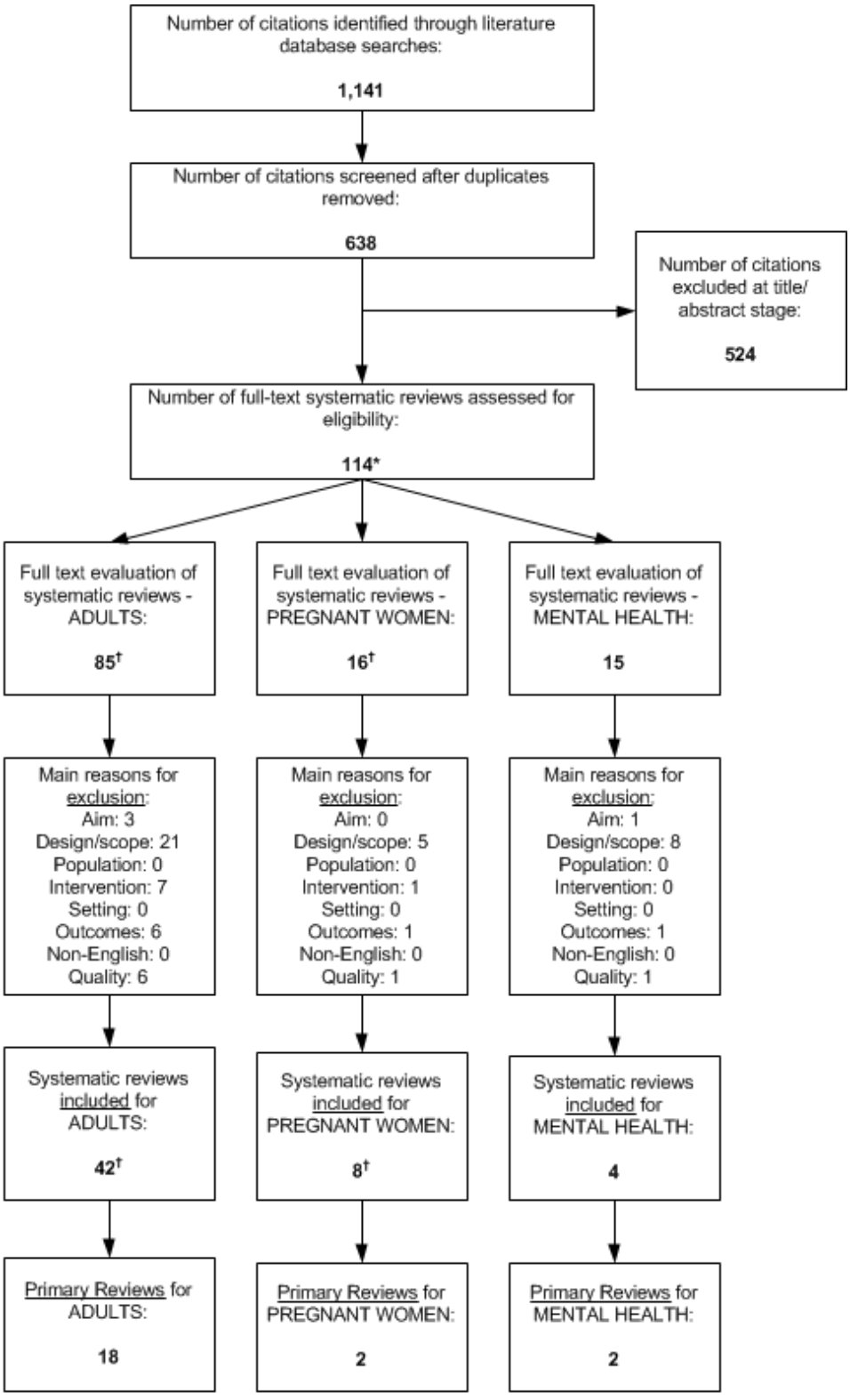
Appendix B Table 2. Adapted AMSTAR Quality Rating Tool

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review and inclusion criteria should be clearly stated.	☐ Yes ☐ No
2a. Was there dual study selection? There should be at least two study selectors/full-text reviewers and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No
2b. Was there dual data extraction? There should be at least two data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. Give "mostly" if there is no mention of search terms, date, or supplemental searches.	☐ Yes ☐ Mostly ☐ No
~~**4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?**~~ ~~The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.~~	
5a. Was a list of studies included provided? A list of included studies should be provided.	☐ Yes ☐ No
5b. Was a list of excluded studies provided? A list of excluded studies should be provided.	☐ Yes ☐ No
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed (e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases) should be reported.	☐ Yes ☐ Mostly ☐ No
7. Was the scientific quality of the included studies assessed and documented? 'A priori methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. Give "no" if only mentioned as a potential limitation but not discussed in terms of how it may or may not affect conclusions or interpretation.	☐ Yes ☐ No

Appendix B Table 2. Adapted AMSTAR Quality Rating Tool

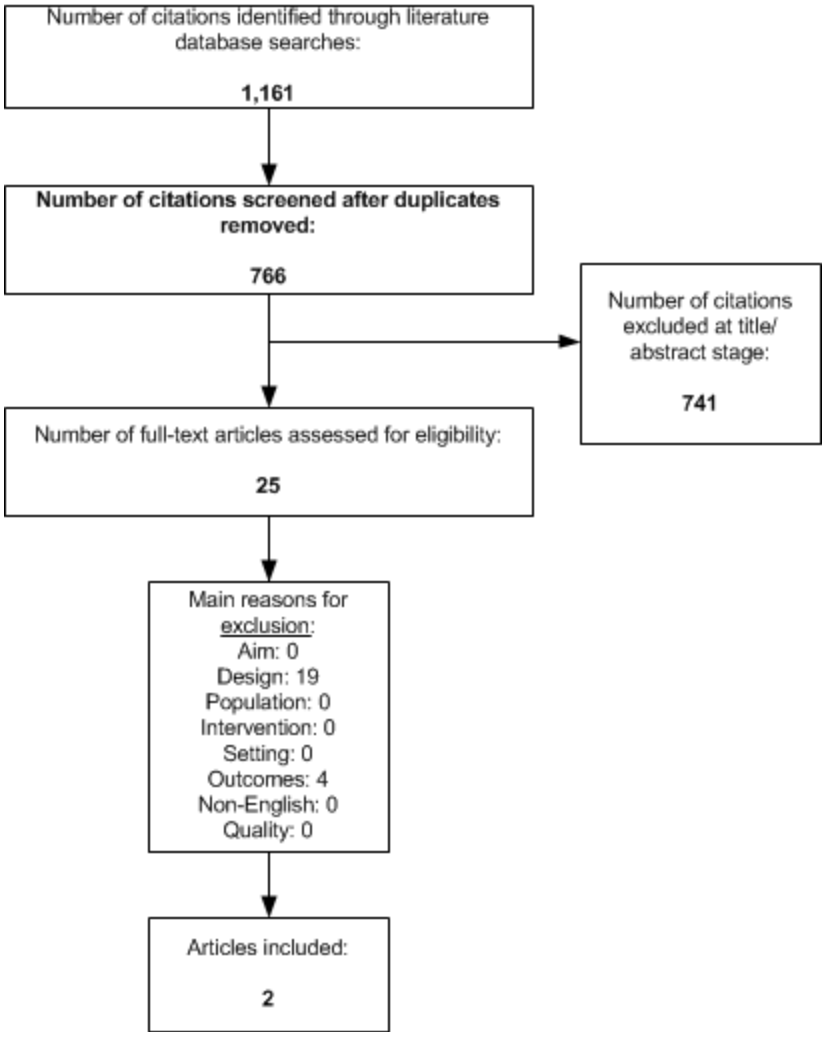
9. Were the methods used to combine the findings of studies appropriate? For pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I-squared). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine)?	☐ Yes ☐ No ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Not applicable
11a. Were potential conflicts of interest/source(s) of support of the systematic review stated? Source(s) of systematic review support should be clearly acknowledged.	☐ Yes ☐ No
11b. Were potential conflicts of interest/source(s) of support of the included studies stated? Source(s) of included studies support should be clearly acknowledged. Give "not applicable" if review only includes behavioral interventions and conflict of interest is not of big concern.	☐ Yes ☐ No ☐ Not applicable
Are there other quality issues of concern? List other issues that cause you to question the trustworthiness of the review.	

Appendix B Figure 1. Literature Flow Diagram: Systematic Reviews

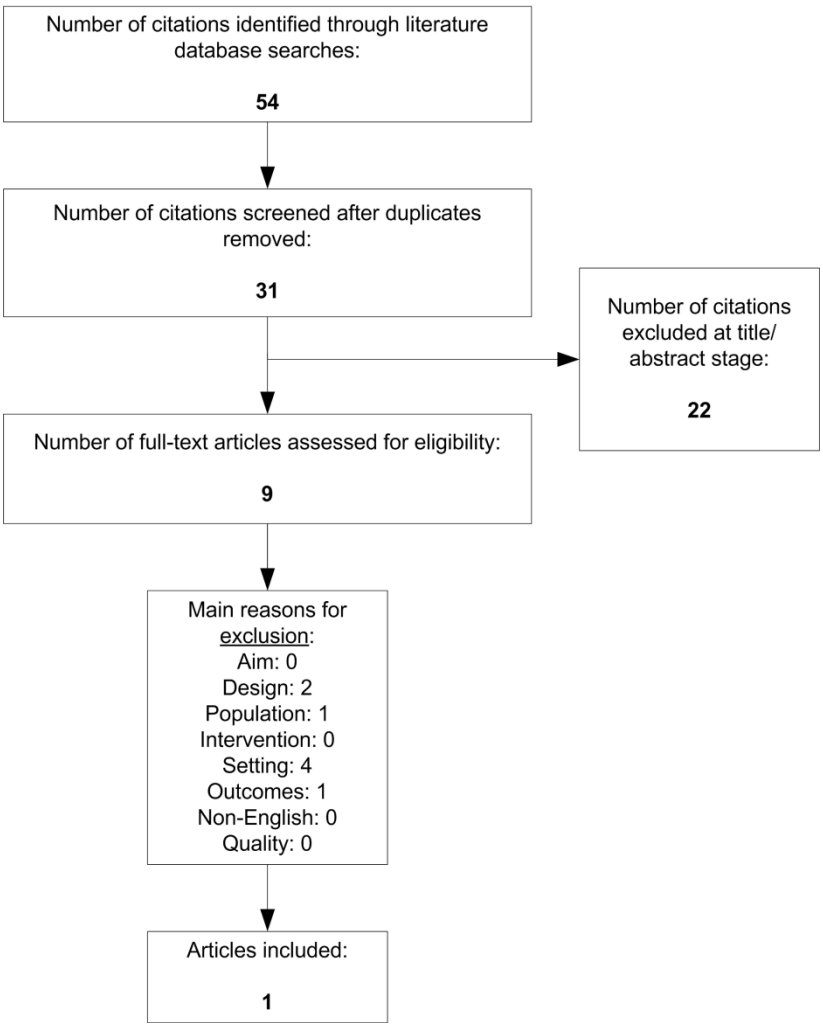


* Two reviews included both adults and pregnant women
† Reviews can be counted in multiple intervention areas

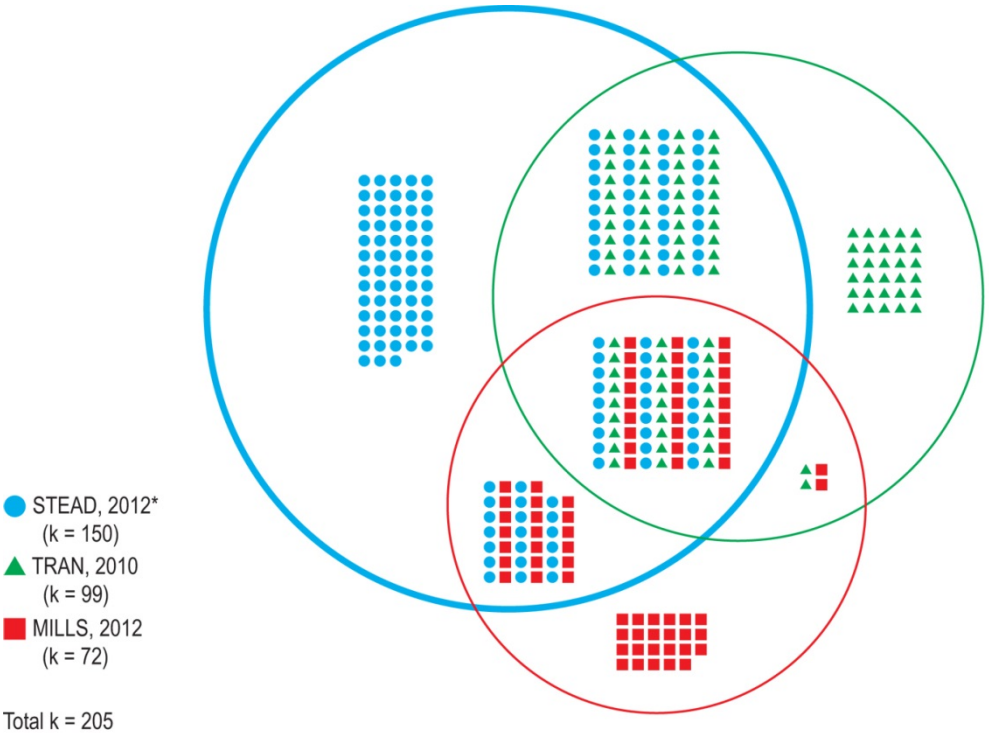
Appendix B Figure 2. Literature Flow Diagram: Primary Evidence on Electronic Nicotine Delivery Systems



Appendix B Figure 3. Literature Flow Diagram: Primary Evidence on Pharmacotherapy in Pregnant Women



Appendix C Figure 1. Overlap in Included Studies in Existing Systematic Reviews on the Effectiveness of Nicotine Replacement Therapy Among Adults

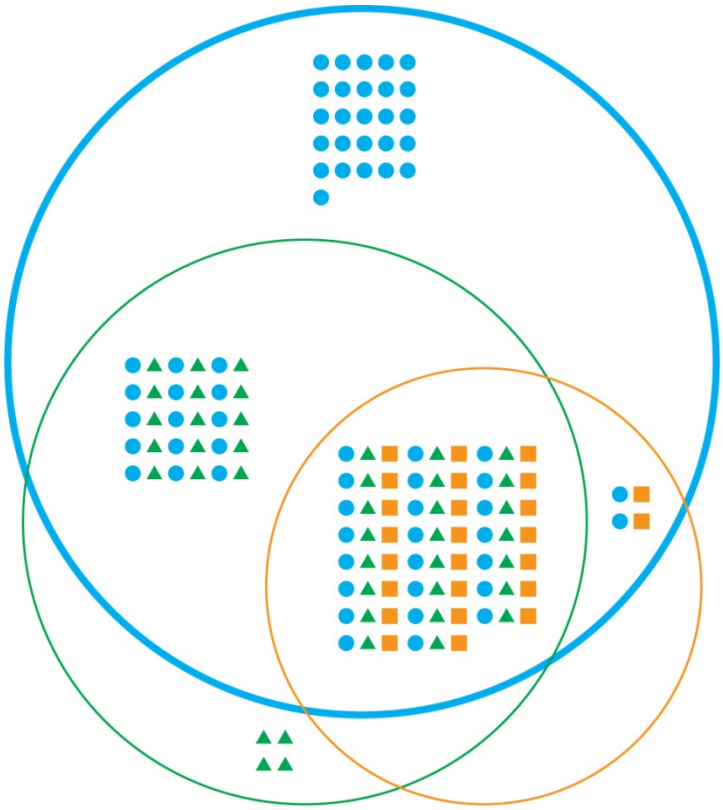


Total k = 205

- Bolin 1999
- Brantmark 1973
- Br Thor Society 1983
- Bullen 2010
- Campbell 1987
- Campbell 1991
- CEASE 1999
- Clavel 1985
- Clavel-Chapelon 1992
- Coleman 2012
- Dautzenberg 2001
- Ehrsam 1991
- Etter 2009
- Fagerstrom 1984
- Fee 1982
- Garcia 1989
- Gariti 2009
- Goldstein 1989
- Gross 1995
- Hilleman 1994
- Huber 1988
- Hughes 1990
- Hughes 1991
- Hughes 1999
- Hughes 2010
- Jensen 1991
- Jorenby 1995
- Kalman 2006
- Killen 1990
- Kornitzer 1987
- Kralikova 2002
- Leischow 1996
- Leischow 1999
- Leischow 2004
- Llivina 1988
- Malcolm 1980
- Marshall 1985
- McGovern 1992
- Mori 1992
- Nakamura 1990
- Nebot 1992
- Ockene 1991
- Ortega 2011
- Otero 2006
- Page 1986
- Puska 1979
- Puska 1995
- Rose 1994
- Rose 1998
- Rose 2006
- Rose 2009
- Rose 2010
- Roto 1987
- Russell 1983
- Schneider 1985
- Schnoll 2010a
- Schnoll 2010b
- Smith 2009
- Tonnesen 2012
- Villa 1999
- Wittchen 2011
- Wong 1999
- Zelman 1992
- Ahluwalia 2006
- Areechon 1988
- Blondal 1989
- Blondal 1997
- Bollinger 2000a
- Cooper 2005
- Fagerstrom 1982
- Fortmann 1995
- Garvey 2000
- Gilbert 1989
- Glover 2002
- Hall 1985
- Hall 1987
- Hall 1996
- Harackiewicz 1988
- Herrera 1995
- Hjalmarson 1984
- Hjalmarson 1994
- Hjalmarson 1997
- Hughes 1989
- ICRF 1994
- Jamrozik 1984
- Jarvis 1982
- Killen 1984
- Lerman 2004
- Niaura 1994
- Niaura 1999
- Oncken 2008
- Pirie 1992
- Richmond 1993
- Schneider 1995
- Schneider 1996
- Segnan 1991
- Shiffman 2009
- Sutherland 1992
- Tonnesen 1988
- Tonnesen 1993
- Tonnesen 2006
- Wallstrom 2000
- Wennike 2003
- Alterman 2001
- Baker 2006
- Batra 2005
- Bock 2008
- Bollinger 2007
- Clavel-Chapelon 1997
- Fortmann 1988
- Ginsberg 1992
- Hill 1993
- Kinnunen 2008
- Lacasse 2008
- Lando 1997
- Lifrak 1997
- Malcolm 1983
- Martin 1997
- Mohiuddin 2007
- Nagle 2005
- Okuyemi 2007
- Pack 2008
- Reid 2008
- Rennard 2006
- Richmond 2007
- Rodriguez-Artalejo 2003
- Schneider 1983
- Simon 1997
- Simon 2003
- Solomon 2000
- Stein 2006
- Wakefield 2004
- Wiggers 2006
- Campbell 1996
- Cinciripini 1996
- Croghan 2003
- Daughton 1991
- Daughton 1998
- Davidson 1998
- Fiore 1994
- Glavas 2003
- Hand 2002
- Hays 1999
- Hughes 2003
- Hurt 1994
- Killen 1997
- Lewis 1998
- Molyneux 2003
- Moolchan 2005
- Oncken 2007
- Paoletti 1996
- Pollak 2007
- Sachs 1993
- Shiffman 2002
- Stapleton 1995
- TNSG 1991
- Tonnesen 1991
- Tonnesen 2000
- Westman 1993
- Wisborg 2000
- Aubin 2008
- Chou 2004
- Dalsgareth 2004
- Daughton 1999
- Doll 1994
- Etter 2002
- Gallagher 2007
- Hanson 2003
- Hatsukami 2004
- Hollis 2007
- Hotham 2006
- Levin 1994
- Merz 1993
- Myung 2007
- Nilsson 1996
- Rigotti 2009
- Sadr Azodi 2009
- Schauffler 2001
- Smith 2003
- Swanson 2003
- Tsukahara 2010
- Uyar 2007
- Yudkin, 1994
- Abelin 1989
- Ahluwalia 1998
- Blondal 1999
- Bohadana 2000
- Buchkremer 1988
- Cooney 2009
- Dale 1995
- Gourlay 1995
- Hurt 1990
- Jorenby 1999
- Joseph 1996
- Killen 1999
- Kornitzer 1995
- Perng 1998
- Piper 2007
- Piper 2009
- Prapavessis 2007
- Richmond 1994
- Schuurmans 2004
- Sonderskov 1997
- Russell 1993
- Tonnesen 1999

*Review served as basis for main finding

Appendix C Figure 2. Overlap in Included Studies in Existing Systematic Reviews on the Effectiveness of Bupropion Among Adults



● Hughes, 2014* (k = 66)

▲ Mills, 2012 (k = 42)

■ Tran, 2010 (k = 25)

Total k = 70

- ● Cinciripini 2013
- ● Collins 2004
- ● Cox 2012
- ● Croghan 2007
- ● Dalsgaro 2004
- ● Eisenberg 2013
- ● Evins 2008
- ● Ferry 1992
- ● Ferry 1994
- ● Gariti 2009
- ● Gorecka 2003
- ● Hall 2011
- ● Hays 2009
- ● Kalman 2011
- ● Levine 2010
- ● Piper 2009
- ● Planer 2011
- ● Rose 2013
- ● Rovina 2009
- ● Schnoll 2010
- ● Selby 2003
- ● Siddiqi 2013
- ● Smith 2009
- ● SMK 2001
- ● Stapleton 2013
- ● Wittchen 2011

- ● ▲ ■ Aubin 2004
- ● ▲ ■ Brown 2007
- ● ▲ ■ Evins 2001
- ● ▲ ■ Evins 2005
- ● ▲ ■ Fossati 2007
- ● ▲ ■ George 2002
- ● ▲ ■ Gonzales 2001
- ● ▲ ■ Haggstram 2006
- ● ▲ ■ Hall 2002
- ● ▲ ■ Hatsukami 2004
- ● ▲ ■ Hertzberg 2001
- ● ▲ ■ Holt 2005
- ● ▲ ■ Hurt 1997
- ● ▲ ■ McCarthy 2008
- ● ▲ ■ Muramoto 2007
- ● ▲ ■ Piper 2007
- ● ▲ ■ Rigotti 2006
- ● ▲ ■ Tashkin 2001
- ● ▲ ■ Tonnesen 2003
- ● ▲ ■ Tonstad 2003
- ● ▲ ■ Uyar 2007
- ● ▲ ■ Wagena 2005
- ● ▲ ■ Zellweger 2005

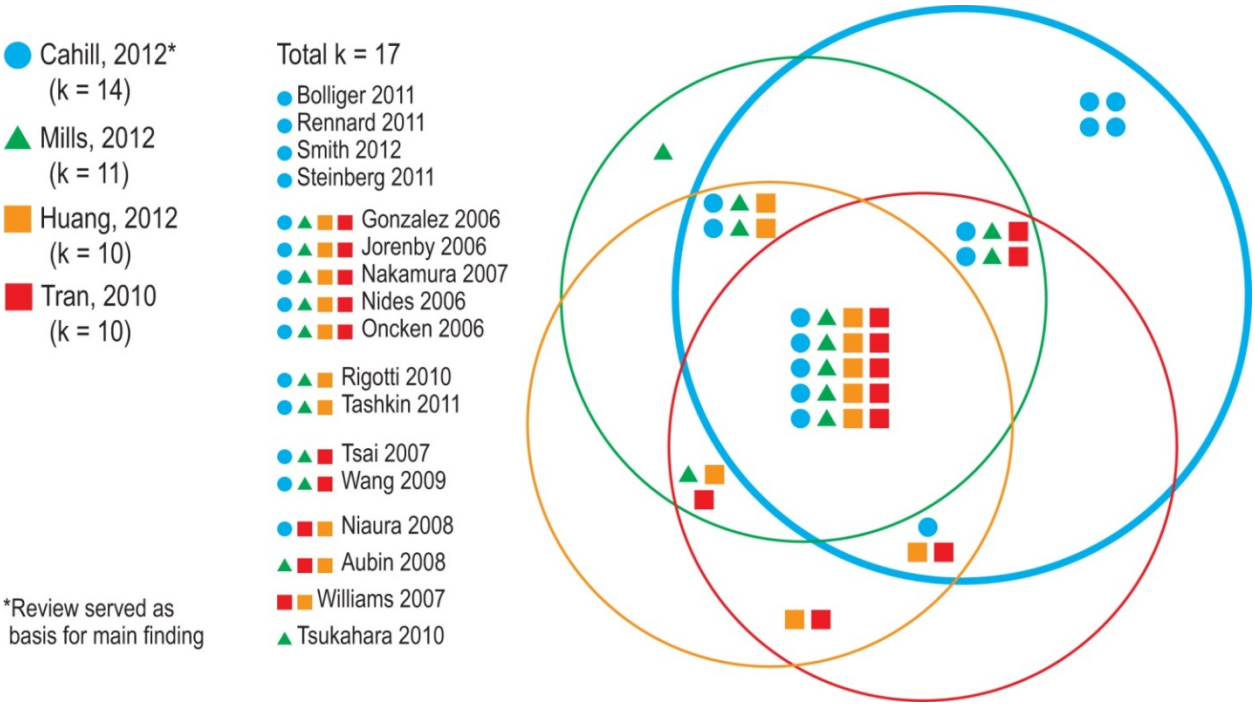
- ● ▲ Covey 2007
- ● ▲ Dalsgareth 2004
- ● ▲ Evins 2007
- ● ▲ George 2008
- ● ▲ Gonzales 2006
- ● ▲ Grant 2007
- ● ▲ Hays 2001
- ● ▲ Hurt 2003
- ● ▲ Jorenby 1999
- ● ▲ Jorenby 2006
- ● ▲ Killen 2004
- ● ▲ Killen 2006
- ● ▲ Myles 2004
- ● ▲ Nides 2006
- ● ▲ Schmitz 2007

- ● ■ Ahluwalia 2002
- ● ■ Simon 2009

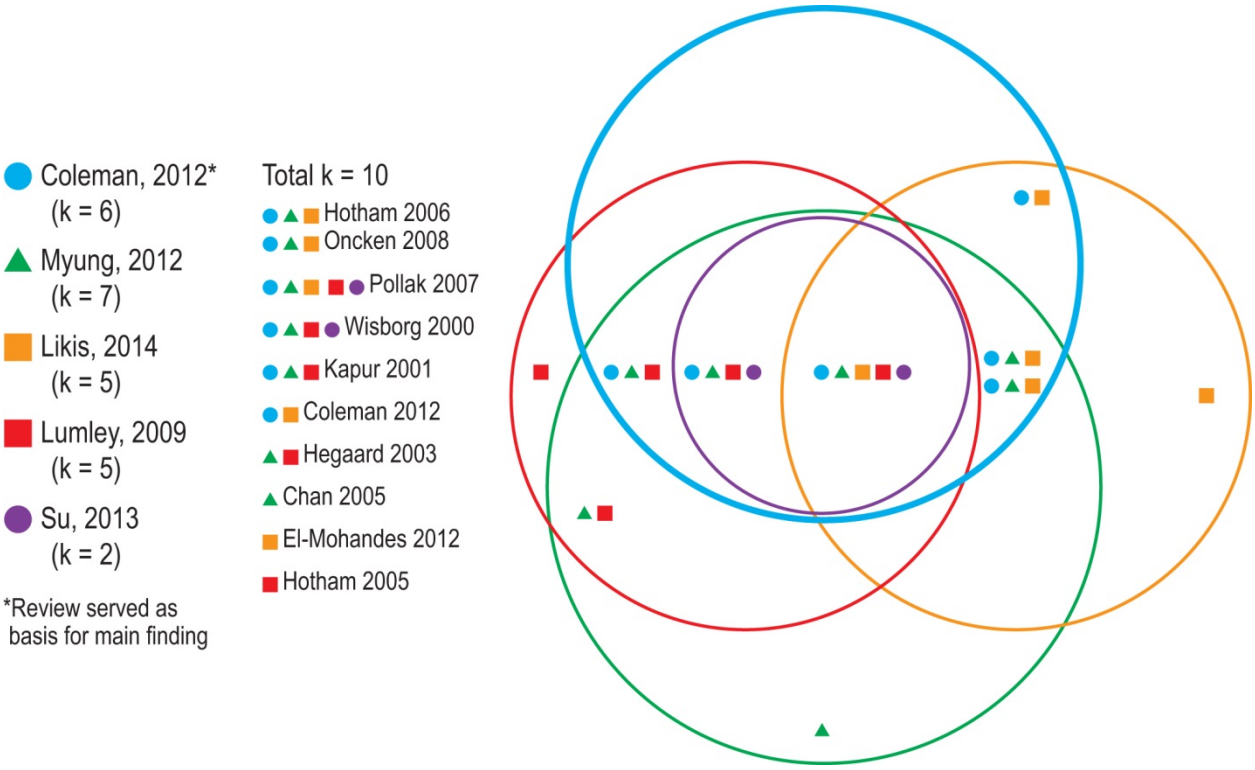
- ▲ Lerman 2002a
- ▲ Lerman 2002b
- ▲ Simon 2004
- ▲ Swanson 2003

*Review served as basis for main finding

Appendix C Figure 3. Overlap in Included Studies in Existing Systematic Reviews on the Effectiveness of Varenicline Among Adults



Appendix C Figure 4. Overlap in Included Studies in Existing Systematic Reviews on the Effectiveness of Pharmacotherapy Among Pregnant Women



Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Abdullah 2005											1	1															
Abroms 2008															1	1		1								1	
Ahijevych & Wewers 1995																						1					
Ahluwalia 1998																						1					
Ahluwalia 1999																											
Ahluwalia 2002																						1					
Ahluwalia 2006							1															1					
Al-Chalabi 2008																1											
Allen 1996		1																									
Allen 1998						1																					
Alterman 2001		1				1														1							
An 2006	1										1																
An 2008														1	1	1	1	1	1							1	
Andrews 1999				1																							
Andrews 2004																											
Andrews 2007																						1					
Antoniou 2005																											
Ard 2008																											
Ardron 1988			1			1																					
Ashraf 2009																											1
Audrain 1997																											
Aveyard 1999									1									1									
Aveyard 2003		1				1			1	1	1	1															
Babamoto 2009																											
Baker 2006	1						1																				
Bakkevig 2000						1																					
Barbarin 1978																											
Barkley 1977																											
Becker 2005																							1				

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Becona 2001a										1																		
Becona 2001b										1																		
Berman 1995										1																		
Betson 1997			1																									
Betson 1998										1																		
Bier 2002																												
Binnie 2007	1			1																								
Bize 2010																												
Bobo 1998									1																			
Bock 2005																												
Bock 2008								1																				
Bolman 2002		1			1																							
Borland 2001											1	1																
Borland 2003									1	1	1	1				1		1										
Borland 2004									1	1						1		1										
Borland 2008											1																	
Borland 2012													1															
Borrelli 2005		1					1	1																				
Bovet 2002																												
Boyle 1992																					1							
Boyle 2004																					1							
Boyle 2007											1									1								
Boyle 2008																					1							
Bramley 2005a																								1	1			
Brandstein 2011	1																											
Brendryen 2008a														1		1	1		1									
Brendryen 2008b														1		1	1	1	1									
Brown 1992						1					1	1																
Brown 2003							1																					

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
BTS 1983										1																	
BTS 1990			1		1	1																					
Buffels 2006																											
Bullen 2010																							1				
Burling 1989										1						1		1									
Burling 1991																											
Burt 1974			1		1																						
Bushnell 1997																				1							
Butler 1999			1				1	1																			
Cai 2000																											
Campbell 1986										1																	
Campbell 1998		1																									
Campbell 1999																											
Campbell 2002																											
Campbell 2004																											
Canga 2000		1																									
Carlson 2000																											
Carlson 2003																											
Carlsson 1997		1																									
Carmody 2008																											
Chan 1988																									1		
Chan 2010	1																										
Chan 2012		1																									
Chiang 2009																											
Chouinard 2005	1	1				1			1		1																
Ciccolo 2011																											
Cigrang 2002								1													1						
Cinciripini 2010																											
Circo 1985																											

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Clark 2004										1				1													
Clavel & Benhamou 1985																											
Clavel 1992																											
Clavel-Chapelon 1997																											
Cohn 2000																											
Colby 1998							1																				
Colby 2005							1																				
Cooney 2007	1																										
Cooper 2005																											
Cossette 2011		1									1																
Cottraux 1983																											
Cropsey 2008																											
Cuckle 1984										1																	
Cummings 1988										1																	
Cummings 1995																					1						
Curry 1988						1																					
Curry 1991										1						1											
Curry 1995						1			1	1	1	1				1											
Curry 2003		1						1																			
Dale 2001																											1
Dale 2002																					1						
Dale 2007																					1						
Darity 1998																											
Darity 2006																						1					
Davies 1992		1								1																	
Davies 2005									1																		
Davis 1984										1																	
Davis 1992										1																	
DeBate 2004																						1					

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
DeBusk 1994		1																									
Demers 1990			1		1																						
deVries 2006					1																						
deVries 2008										1																	
Dijkstra 1998									1	1						1											
Dijkstra 1998																1											
Dijkstra 1999									1	1						1											
Docherty 2003																											
Doolan 2008																											1
Dornelas 2000								1																			
Dornelas 2006																											
Dornelas 2007																											
Duffy 2006	1	1									1																
Ebbert 2007				1							1										1						
Ebbert 2009																					1						
Ebbert 2010a																					1						
Elder 2005																											
Elfeddali 2012														1													
Elkins 2006																											
Ellerbeck 2009											1									1							
Emmons 2001							1																				
Emmons 2005	1										1																
Erickson 1983																											
Ershoff 1999																1											
Escoffery 2004									1						1												
Etter 2001																1		1									
Etter 2004									1	1																	
Etter 2005														1		1	1										
Etter 2009b																1											

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Fagerstrom 1984			1																								
Fagerstrom 2010																					1						
Family Heart 1994		1																									
Fang 2006																						1					
Fee 1977																											
Feeney 2001		1																									
Ferguson 2012											1																
Fiore 2004						1					1									1							
Fisher 1998																											
Fitzgibbon 2005																											
Floter 2009											1																
Flynn 2010																						1					
Fortmann 1995										1																	
Free 2008																											
Free 2009													1			1											
Free 2011													1														
Fritz 2012																											
Froelicher 2004		1																									
Gala 2008															1												
Gandhi 2009																											
Gansky 2005				1																	1						
Garcia 2000						1																					
Gariti 2009																				1							
Gebauer 1998																											
Georgiou 1998																											
Georgiou 1999																											
Gershon Grand 2007																											
Gielen 1997																											
Gilbert 1992			1																								

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Gilbert 2006											1	1															
Gilbert 2007																1		1									
Gilbert 2013										1																	
Gilbey & Neumann 1977																											
Gillams 1984																											
Ginsberg 1992																				1							
Girgis 2011											1																
Glasgow 1981						1				1																	
Glasgow 2000						1		1																			
Gonzales 2006																											
Gordon 2010a				1																							
Gordon 2010b				1																							
Graham 2011											1			1													
Gritz 1992										1																	
Groner 2000					1																						
Hajek 2002		1				1																					
Hall 1985																				1							
Hall 1987																				1							
Hall 1994																				1							
Hall 1998																				1							
Hall 2002	1					1														1							
Hall 2006	1															1											
Hall 2009																				1							1
Halpin 2006											1																
Han 2006																											
Hanioka 2010	1			1																							
Hannover 2009									1																		
Hanssen 2007		1																									
Hanssen 2009											1																

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Harackiewicz 1988										1																	
Harding 2005																											
Hasuo 2004		1																									
Hatsukami 1996																					1						
Hatsukami 2000																					1						
Haug 1994			1		1																						
Haug 2009																1											
Haug 2011														1													
He 1997																											
He 2001																											
Hellmann 1988																										1	
Henderson 2004																											
Hennrikus 2002											1																
Hennrikus 2005		1				1		1	1																		
Hensel 1995																											
Herman 2003																										1	
Hernandez-Lopez 2009																											
Higashi 1995			1																								
Hilberink 2005		1	1		1																						
Hill 1985																											
Hill 1993																											1
Hishida 2010																											
Hodge 1999																											
Hokanson 2006							1	1																			
Hollis 1993		1				1				1																	
Hollis 2005							1		1																		
Hollis 2007	1							1			1									1							
Holmes-Rovner 2008											1																
Holt 2005																								1			

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Horn 2007							1																				
Hoving 2010										1																	
Howard-Pitney 1999																					1						
Huber 2003																				1							
Humerfelt 1998										1																	
Humfleet 2013														1													
Hyman 1986																											
Hyman 2007							1																				
Hymowitz 1996																											
Hymowitz & Eckholdt 1998																											
ICRF 1994										1																	
Ingersoll 2009							1																				
Ito 2006																											
Ivers 2003																								1			
Jackson 2004						1																					
Jamrozik 1984			1		1																						
Janz 1987		1	1		1					1																	
Japuntich 2006														1		1	1	1	1								
Jason 1988																						1					
Jenkins 1997																											
Jiang 2007		1																									
Johnson 1997																								1			
Jorenby 1995						1														1							
Jorenby 2006																											
Joyce 2008											1																1
Juarranz Sanz 1998	1																										
Kalman 2001																											
Katz 2004	1										1																
Kendrick 1995																											

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Kerr 2008																											
Keyserling 2002																											
Killen 1990										1																	
Killen 1997										1																	
Killen 2008																				1							
Kim 2005		1				1																					1
Kinnunen 2008																											
Klesges 1999																											
Klesges 2006																										1	
Knight 2004																											
Kottke 1989										1																	
Kotz 2009	1																										
Kreuter 1996																1											
Kreuter 2005																											
Labadie 1983																											
Lacey 1991																						1					
Lacroix 1977																											
Lagrue 1980																											
Lambe 1986																											
Lamontagne 1980																											
Lancaster 1999		1				1																					
Lando 1975																											
Lando 1988										1																	
Lando 1991										1																	
Lando 1992											1	1															
Lando 1997						1					1									1							
Lando 2007				1																							
Lang 2000			1																								
Larson 2009																						1					

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Lawrence 2003																1											
Lawrence 2005									1																		
Ledwith 1984										1																	
Leischow 1996																											
Lennox 1998									1																		
Lennox 2001									1	1						1											
Lerman 2004																											
Leung 1991																											
Lewis 1998	1	1																									
Li 1984			1			1																1					
Li 2009																											
Lichtenstein 1973																											
Lichtenstein 2000										1	1	1															
Lichtenstein 2008										1	1	1															
Lifrak 1997																				1							
Lillington 1995																											
Lipkus 1999										1	1											1					
Lipkus 2004							1				1																
Lloyd-Richardson 2009																				1							
Loke & Lam 2005																											
Lopes 1995																											
Lowe 1998						1																					
Luna 2004																									1		
Lung Health Study	1																										
Ma 2004																						1					
MacLeod 2003											1									1							
Maguire 2001						1																					
Maher 2007																											
Malchodi 2003						1																					

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Manfredi 1999																											
Manfredi 2004									1																		
Marcus 1991																											
Marcus 1995																											
Marcus 1999																											
Marcus 2005																											
Marshall 1985			1																								
Martin & Waite 1981																											
Martin 1997																											
Mason 2012														1													
Matthews 2009																						1					
May 2006																											
McAlister 1992																											
McBride 1999a									1		1	1															
McBride 1999b											1																
McBride 2002																						1					
McBride 2004											1																
McCarthy 2008	1																			1							
McClure 2005								1			1																
McClure 2009																											
McClure 2011											1																
McDonnell 2011														1													
McDowell 1985			1		1																						
McFall 1993										1	1																
McFall 2010																											1
McKay 2008														1		1	1		1								
McPhee 1995																											
Mermelstein 2003									1																		
Mermelstein 2006																		1									

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Metz 2007											1																
Meyer 2008			1						1	1						1											
Meyer 2012			1							1																	
Meysman 2010		1							1																		
Miguez 2002						1					1	1															
Miguez 2008											1	1															
Miller 1997		1				1					1																
Mogielnicki 1986						1																					
Mohiuddin 2007	1																										
Molyneux 2003	1				1	1																					
Morgan 1996			1		1																						1
Munoz 1997																											
Munoz 2006														1			1		1								
Munoz 2009														1		1	1										
Murphy 2005																											
Murray 2001																											
Nagle 2005		1																									
Nakamura 2004									1																		
Nebot 1989			1																								
Nebot 1992		1																									
Nevid 1997																											
Newton 2004																											
Nohlert 2009				1																							
Nollen 2007										1												1	1				
Obermayer 2004															1												
Ockene 1991	1		1								1									1							
Oenema 2008														1		1	1										
Okuyemi 2007	1																										
O'Loughlin 1997																											

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Omenn 1988						1				1																	
O'Neill 2000									1							1										1	
Orleans 1991										1	1	1															
Orleans 1998										1	1											1	1				
Orleans 2000										1						1											1
Osinubi 2003											1																
Ossip-Klein 1991											1																
Ossip-Klein 1997											1	1															1
Otero 2006	1																			1							
Owen 1989										1						1											
OXCHECK 1994		1																									
Page 1986			1																								
Pallonen 1994									1	1																	
Parekh 2014										1																	
Parker & Mok 1977																											
Parkes 2008																											
Patten 2004									1																		
Patten 2006														1				1	1								
Pederson 1975																											
Pederson 1979																											
Pederson 1980																											
Pederson 1983										1																	
Perez-Stable 1991																											
Persson 2006							1																				
Pickworth 1997																											
Pieterse 2001			1		1				1																		
Pike 2007																1	1	1	1								
Pisinger 2010																	1										
Porter 1972			1																								

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Prapavessis 2007																											
Prochaska 1993									1	1	1	1				1											
Prochaska 2001a									1	1						1		1									
Prochaska 2001b									1	1	1	1				1		1									
Prochaska 2004									1	1						1											
Prochaska 2005									1	1						1											
Prochaska 2008							1		1							1	1		1								
Prokhorov 2008							1		1						1	1		1								1	
Prue 1983										1																	
Quist-Paulsen 2003		1			1																						
Rabius 2004						1					1	1														1	
Rabius 2007											1	1															
Rabius 2008														1													
Rabkin 1984																											
Ratner 2004	1	1																									
Reid 1999											1									1							
Reid 2003	1																										
Reid 2007											1					1											
Reid 2008	1																										
Reitzel 2010																											
Resnicow 1997										1												1					
Rescinow 2009																											
Rice 1994		1								1																	
Richmond 1986			1		1	1																					
Richmond 2006																											
Rigotti 1994		1				1																					
Rigotti 1997								1																			
Rigotti 2006											1																
Riley 2002																1											

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Riley 2008															1												
Rimer 1994											1	1															1
Risser 1990		1																									
Rodgers 2005													1		1	1											
Rodondi 2012																											
Rodriguez 2003	1																										
Rohsenow 2002							1																				
Romand 2005						1																					
Rose 1978			1		1																						
Roski 2003											1																
Rovina 2009																				1							
Royce 1995																						1					
Russell 1979			1		1																						
Russell 1983			1		1																						
Russell 1988																											
Sadr Azodi 2009	1																										
Sanders 1989		1			1	1																					
Sanz-Pozo 2006		1																									
Sawicki 1993						1																					
Schauffler 2001	1																										
Scheuer 2005																											
Schmitz 2007																											
Schneider 1990																1											
Schnoll 2003			1																								
Schofield 1999										1																	
Schorling 1997																						1					
Schumann 2006									1																		
Schumann 2008										1						1		1									
Secker-Walker 1994						1																					

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Secker-Walker 1998						1																					
Segnan 1991	1		1			1																					
Severson 1997			1																								
Severson 1998				1	1																1						
Severson 2000																					1						
Severson 2007																					1						
Severson 2008																					1						
Severson 2009				1																	1						
Shahab 2011																											
Shelley 2008																						1					
Shiffman 2000																1		1									
Shiffman 2001																1		1									
Shiffman 2006																											
Sias 2008																											
Simmons 2007																										1	
Simon 1997	1																										
Simon 2003																				1							
Sims 2013											1																
Sippel 1999																											
Skewes 2006																										1	
Slama 1990			1		1	1																					
Slama 1995			1																								
Slovinec 2005						1																					
Smeets 2007																1											
Smit 2012														1													
Smith 2001							1													1							
Smith 2004										1	1	1															
Smith 2013											1																
Solomon 2000											1									1							

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Solomon 2005											1									1								
Sood 2009											1																	
Sorensen 2007a											1																	
Soria 2006							1	1																				
Stanton 2004																												
Stein 2006								1												1								
Steiner 1982																												
Steptoe 1999		1																										
Stevens 1995				1																	1							
Stewart 1982			1		1																							
Stoddard 2008														1		1	1											
Stotts 2002									1		1																	
Stotts 2003																					1							
Strecher 1994																1												
Strecher 2005a										1						1												
Strecher 2005b														1		1	1	1	1									
Strecher 2005c																1												
Strecher 2008														1		1	1											
Sutton & Gilbert 2007										1						1		1										
Swan 2003											1									1								
Swan 2010											1			1		1				1								
Swartz 2006														1		1	1	1	1									
Sykes 2001										1																		
Tappin 2000						1																						
Tappin 2005					1	1																						
Taylor 1988																												
Taylor 1990		1			1	1																						
Te Poel 2009														1														
Terazawa 2001		1																										

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Tevyaw 2009																										1	
Thompson 1988			1							1																	
Thompson 1993									1		1																
Thomsen 2010	1																										
Tian 1996																											
Tindle 2006																											
Tonnesen 1996		1			1	1																					
Tonnesen 2006	1	1																		1							
Tzelepis 2011											1																
Unrod 2007			1																								
Ussher 2003																											
van der Aalst 2012										1																	
Vandevenne 1985																											
Velicer 1999									1	1						1											
Velicer 2006	1									1	1					1											
Vetter 1990		1	1		1	1																					1
Vial 2002	1																										
Vibes 1977																											
Villebro 2008	1																										
Voorhees 1996																						1					
Waite & Clough 1998																											
Wakefield 2004	1						1																				
Walker 1985																											
Walker 2011																							1				
Walker 2012																							1				
Walsh 1999				1																	1						
Walsh 2003				1																	1						
Walsh 2010																					1						
Wang 1994									1																		

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Wangberg 2011														1													
Weissfield & Holloway 1991						1																					
Webb 2008																						1					
Webb 2009																						1					
Webb 2013										1																	
Wetter 2007																							1				
Wewers 2000	1																										
Wewers 2009	1																										
White 1998																											
White 2007																											
Whittaker 2011													1											1			
Wiggers 2006																				1							
Willemsen 2006										1																	
Williams 1988																											
Williams 2002			1																								
Williams 2006																											
Williams 2010																				1							
Wilson 1982			1																								
Wilson 1988	1																										
Wilson 1990			1		1																						
Wilson 2008							1																				
Windsor 1993																											
Windsor 2000						1																					
Wing 2010																											
Wolfenden 2005																1											
Wong 2008																						1					
Wood 2008		1																									
Woodruff 2002																							1				
Woodruff 2007							1							1													

Appendix C Table 1. List of Included Studies for Behavioral Intervention Reviews: Adults

Intervention Type **1=Combined** **2=Behavioral counseling** **3=Print** **4=Phone** **5=Computer** **6=Behavioral adjunct** **7=Special populations**	1	2	2	2	2	2	2	2	2	3	4	4	4	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Reviews **Included Studies**	Stead, 2012*	Rice, 2013*	Stead, 2013a*	Carr, 2012	Bodner, 2009	Mottillo, 2009	Hettema, 2010	Lai, 2010	Cahill, 2010	Hartmann-Boyce, 2014	Stead, 2013c*	Tzelepis, 2011	Whittaker, 2012*	Civljak, 2013*	Brown, 2013	Chen, 2012	Hutton, 2011	Myung, 2009	Shahab, 2009	Stead, 2013b*	Ebbert, 2011	Liu, 2013	Nierkens, 2013	Johnston, 2013	Carson, 2012	Villanti, 2010	Zbikowski, 2012
Wu 2007																											
Wu 2009																				1		1					
Yeh 2009																											
Yilmaz 2006					1																						
Yiming 2000																											
Young 2008									1		1																
Zanis 2011																									1		
Zernig 2008																											
Zhang 2013																											
Zhu 1996											1	1															
Zhu 2002											1	1															
Zhu 2012											1																
	41	**49**	**41**	**14**	**29**	**50**	**23**	**14**	**41**	**74**	**77**	**23**	**5**	**27**	**8**	**60**	**16**	**22**	**11**	**38**	**25**	**28**	**5**	**5**	**4**	**14**	**13**

Appendix C Table 2. List of Included Studies for Behavioral Intervention Reviews: Pregnant Women

Reviews / Included Studies	Chamberlain 2013	Fillon 2011	Hettema 2010	Likis 2013	Lumley 2009	Su 2013
Albrecht 1998	1				1	
Albrecht 2006	1			1		1
Baric 1976	1				1	
Bauman 1983	1			1	1	
Belizan 1995	1				1	
Brandon 2012						1
Bullock 1995	1				1	
Bullock 2009	1	1		1		1
Burling 1991	1			1	1	
Byrd 1993	1					
Campbell 2006	1				1	
Cinciripini 2000	1				1	
Cinciripini 2010	1			1		1
Cook 1995	1					
Cope 2003	1			1	1	
deVries 2006					1	1
Donatelle 2000	1			1	1	1
Donovan 1977	1				1	
Dornelas 2006	1			1	1	
Dunkley 1997	1				1	
Eades 2012	1					
El-Mohandes 2011	1					1
Ershoff 1989	1			1	1	
Ershoff 1995				1	1	
Ershoff 1999	1		1	1	1	
Gadomski 2011						1
Gielen 1997	1			1	1	
Graham 1992	1					
Haddow 1991	1				1	
Hajek 2001	1			1	1	
Hartmann 1996	1			1	1	
Haug 1994	1					
Haug 2004	1					
Hegaard 2003	1			1		
Heil 2008	1			1	1	1
Hennrikus 2010	1			1		1
Hiett 2000	1					
Higgins 2004					1	1
Hjalmarson 1991	1			1	1	
Hughes 2000	1					
Jimenez-Muro 2012				1		
Johnson 2000				1		
Kendrick 1995	1			1	1	
Lawrence 2003	1			1	1	
Lawrence 2005						1
LeFevre 1995	1					
Lilley 1986	1				1	
Lillington 1995	1					1
Loeb 1983	1				1	
Lowe 1997	1			1	1	
Lowe 1998					1	
Lowe 2002	1					
MacArthur 1987					1	
Malchodi 2003	1	1		1	1	
Manfredi 1999	1				1	
Mayer 1990	1				1	
McBride 1999	1				1	1
McBride 2004	1					1
McLeod 2004	1				1	

Appendix C Table 2. List of Included Studies for Behavioral Intervention Reviews: Pregnant Women

Reviews / Included Studies	Chamberlain 2013	Fillon 2011	Hettema 2010	Likis 2013	Lumley 2009	Su 2013
Messimer 1989	1					
Moore 1998	1					
Moore 2002	1			1	1	
Morasco 2006						1
Mullen 1990						1
Naughton 2012	1			1		
O'Connor 1992				1	1	1
Olds 1986	1				1	
Olds 2002	1					
Ondersma 2012	1			1		
Panjari 1999	1			1	1	
Parker 2007	1					
Patten 2009	1					
Pbert 2004	1			1	1	1
Peden 2008						1
Petersen 1992	1				1	1
Phillips 2012				1		
Polanska 2004	1				1	
Polanska 2005						1
Price 1991	1			1	1	
RADIUS 1995					1	
Reading 1982	1				1	
Reitzel 2010				1		1
Rigotti 2006	1	1	1	1	1	1
Ruger 2008		1	1	1		
Rush 1992					1	
Secker-Walker 1994	1	1		1	1	1
Secker-Walker 1995				1	1	
Secker-Walker 1997	1			1	1	
Secker-Walker 1998a	1	1		1	1	1
Secker-Walker 1998b				1		
Sexton 1984	1				1	
Solomon 1996					1	
Solomon 2000	1			1	1	
Stotts 2002	1		1	1	1	1
Stotts 2004	1		1			
Stotts 2009	1			1		
Strecher 2000	1				1	
Suplee 2005			1	1		
Tappin 2000	1	1	1		1	
Tappin 2005	1	1	1	1	1	
Thornton 1997	1				1	
Tsoh 2010	1					
Tuten 2012	1			1		
Valanis 2001						1
Valbo 1991					1	
Valbo 1994	1				1	
Valbo 1996	1				1	
Vilches 2009	1					
Wall 1995						1
Walsh 1997	1			1	1	1
Windsor 1985	1			1	1	
Windsor 1993	1			1	1	
Windsor 2000					1	
Windsor 2011	1			1		
Total Studies	86	8	8	50	67	30

Appendix D. Excluded Systematic Reviews List

Code	Definition
AP	Adults – pharmacological
AB	Adults – behavioral
AC	Adults – combined
AM	Adults – mental
PWP	Pregnant women – pharmacological
PWB	Pregnant women – behavioral
PWC	Pregnant women – combined
PPP	Pregnant women – pharmacological (from primary studies search)
ENDS	Electronic nicotine delivery systems

Exclusion Code	Definition
E1	Study aim not relevant
E2a	Not a systematic review
E2b	Does not describe search dates AND search databases AND search string
E2c	Does not indicate criteria used to select studies for inclusion
E2d	Review of reviews
E3a	**Population**: ≥50% of studies included focus on children and adolescents, and stratified results not presented
E3b	**Population:** > 50% of the included studies focus on groups not generalizable to primary care (e.g., COPD), and stratified results not presented
E4	**Intervention**: Not a relevant intervention (e.g., systems-level, broad public health intervention, harm reduction, second-line or off-label medications, relapse prevention)
E5	**Setting**: > 50% of the included studies take place in settings not applicable to primary care (e.g., worksites, specialty care), and stratified results not presented
E6	**Outcomes**: No relevant outcomes (exclude reviews that only report tobacco reduction; reduction in withdrawal symptoms; attitudes, knowledge, beliefs; intentions; etc.)
E7	**Outcome Assessment**: > 50% of the included studies report outcomes at < 6 months follow up, and stratified results not presented (does not apply for KQ3/harms data)
E8	**Country**: > 50% of included studies take place in countries not on the "Very High" list for Human Development: Andorra, Argentina, Australia, Austria, Barbados, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Seychelles, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States
E9	Review published in language other than English
E10	All included studies are included in a more comprehensive, more recent, or higher quality ESR
E11	Poor quality rating

1. Adkison SE, O'Connor RJ, Bansal-Travers M, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. Am J Prev Med 2013 Mar;44(3):207-15. PMID: 23415116. **ENDSE2**
2. Adriaens K, Van GD, Declerck P, et al. Effectiveness of the Electronic Cigarette: An Eight-Week Flemish Study with Six-Month Follow-up on Smoking Reduction, Craving and Experienced Benefits and Complaints. Int J Environ Res Public Health 2014;11(11):11220-48. PMID: 25358095. **ENDSE2**
3. Ahmed AI, Ali AN, Kramers C, et al. Neuropsychiatric adverse events of varenicline: a systematic review of published reports. J Clin Psychopharmacol 2013 Feb;33(1):55-62. PMID: 23277249. **AME2a**
4. Apollonio D, Philipps R, Bero L. Interventions for tobacco use cessation in people in treatment for or recovery from substance abuse. Cochrane Database of Systematic Reviews 2012 **AME2**
5. Asfar T, Ebbert JO, Klesges RC, et al. Do smoking reduction interventions promote cessation in smokers not ready to quit? Addictive Behaviors 2011;36(7):764-8. PMID: 21420791. **ACE4**

6. Baxter, S, Blank, L, Guillaume, L, et al. Systematic review of how to stop smoking in pregnancy and following childbirth. United Kingdom: University of Sheffield School of Health and Related Research (ScHARR); 2009. **PWCE6**
7. Bennett ME, Wilson AL, Genderson M, et al. Smoking Cessation in People with Schizophrenia. Curr Drug Abuse Rev 2013 May 30 PMID: 23721094. **AME2a**
8. Bullen C, McRobbie H, Thornley S, et al. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tob Control 2010 Apr;19(2):98-103. PMID: 20378585. **ENDSE6**
9. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013 Sep 9 PMID: 24029165. **ENDSI1**
10. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329. PMID: 23728690. **APE2d**
11. Cahill K, Stevens S, Lancaster T. Pharmacological treatments for smoking cessation. JAMA 2014 Jan 8;311(2):193-4. PMID: 24399558. **APE2a**
12. Canadian Agency for Drugs and Technologies in Health. Varenicline for smoking cessation in patients with psychiatric illness: a review of the risks. 2010. **AME2a**
13. Canadian Agency for Drugs and Technologies in Health. Smoking cessation interventions for pregnant women and mothers of infants: a review of the clinical effectiveness, safety, and guidelines. 2012. **PWCE2a**
14. Canadian Agency for Drugs and Technologies in Health. Nicotine Replacement Therapy for Smoking Cessation or Reduction: A Review of the Clinical Evidence. 2014. PMID: 24741730. **APE2a**
15. Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. PLoS ONE 2013;8(6):e66317. PMID: 23826093. **ENDSI1**
16. Caponnetto P, Auditore R, Russo C, et al. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. Int J Environ Res Public Health 2013 Feb;10(2):446-61. PMID: 23358230. **ENDSE2**
17. Carim-Todd L, Mitchell SH, Oken BS. Mind-body practices: An alternative, drug-free treatment for smoking cessation? A systematic review of the literature. Drug Alcohol Depend 2013 May 7 PMID: 23664122. **ABE6**
18. Choi K, Forster JL. Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults. Am J Prev Med 2014 Feb;46(2):175-8. PMID: 24439352. **ENDSE2**
19. Coleman T, Agboola S, Leonardi-Bee J, et al. Relapse prevention in UK stop smoking services: current practice, systematic reviews of effectiveness and cost-effectiveness analysis. Health Technology Assessment 2010;14(49):1-152. PMID: 21040645. **ACE4, PWCE4**
20. Coleman T, Chamberlain C, Cooper S, et al. Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. Addiction 2011;106(1):52-61. PMID: 21054620. **PWPE10**
21. Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. New England Journal of Medicine 2012 Mar 1;366(9):808-18. PMID: 22375972. **PPPE8**
22. Dai CL, Sharma M. Between inhale and exhale: yoga as an intervention in smoking cessation. J Evid Based Complementary Altern Med 2014 Apr;19(2):144-9. PMID: 24647095. **ABE6**
23. Dawkins L, Turner J, Hasna S, et al. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. Addictive Behaviors 2012;37(8):970-3. PMID: 22503574. **ENDSE6**
24. Dawkins L, Turner J, Roberts A, et al. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. Addiction 2013 Jun;108(6):1115-25. PMID: 23551515. **ENDSE2**
25. Dornelas E, Oncken C, Greene J, et al. Major depression and PTSD in pregnant smokers enrolled in nicotine gum treatment trial. American Journal on Addictions 2013 Jan;22(1):54-9. PMID: 23398227. **PPPE6**
26. El-Mohandes AA, Windsor R, Tan S, et al. A randomized clinical trial of trans-dermal nicotine replacement in pregnant African-American smokers. Maternal & Child Health Journal 2013 Jul;17(5):897-906. PMID: 22761006. **PPPE8**
27. Ellery, B, Hiller, JE. Quit onQ SMS for smoking cessation support for individuals. 2010. **ABE2a**
28. Etter JF. Electronic cigarettes: a survey of users. BMC Public Health 2010;10:231. PMID: 20441579. **ENDSE2**

29. Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction 2011 Nov;106(11):2017-28. PMID: 21592253. **ENDSE2**
30. Etter JF, Bullen C. A longitudinal study of electronic cigarette users. Addict Behav 2014 Feb;39(2):491-4. PMID: 24229843. **ENDSE2**
31. Fagerstrom K, Nakamura M, Cho HJ, et al. Varenicline treatment for smoking cessation in Asian populations: a pooled analysis of placebo-controlled trials conducted in six Asian countries. Curr Med Res Opin 2010 Sep;26(9):2165-73. PMID: 20666691. **APE2b**
32. Farsalinos KE, Romagna G, Tsiapras D, et al. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. Subst Abuse 2013;7:139-46. PMID: 24049448. **ENDSE2**
33. Farsalinos KE, Romagna G, Tsiapras D, et al. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. Int J Environ Res Public Health 2013 Jun;10(6):2500-14. PMID: 23778060. **ENDSE6**
34. Ferguson J, Docherty G, Bauld L, et al. Effect of offering different levels of support and free nicotine replacement therapy via an English national telephone quitline: randomised controlled trial. BMJ 2012;344:e1696. PMID: 22446739. **PPPE3**
35. Ferron JC, Alterman AI, McHugo GJ, et al. A review of research on smoking cessation interventions for adults with schizophrenia spectrum disorders. Mental Health and Substance Use 2009;2(1):64-79. PMID: none. **AME11**
36. Foulds J, Veldheer S, Berg A. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. Int J Clin Pract 2011 Oct;65(10):1037-42. PMID: 21801287. **ENDSE2**
37. Gierisch JM, Bastian LA, Calhoun PS, et al. Smoking cessation interventions for patients with depression: a systematic review and meta-analysis. Journal of General Internal Medicine 2012;27(3):351-60. PMID: 22038468. **AME10**
38. Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an internet survey. Drug Alcohol Rev 2013 Mar;32(2):133-40. PMID: 22994631. **ENDSE2**
39. Grana R, Popova L, Ling PM. A Longitudinal Analysis of Electronic Cigarette Use and Smoking Cessation. JAMA 2014 Mar 24;174(5):812-3. PMID: 24664434. **ENDSE2**
40. Hajek P, Stead LF, West R, et al. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2009;Issue 1 PMID: 23963584. **ACE4**
41. Hartmann-Boyce J, Stead LF, Cahill K, et al. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2012 reviews. Addiction 2013 Jul 9;108(10):1711-21. PMID: 23834141. **ACE2a**
42. HAYES. Smoking cessation in patients with schizophrenia. 2014. **AME2a**
43. Hayes Inc. Chantix (Varenicline Tartrate) (Pfizer Inc.) for smoking cessation. 2010. **APE2a**
44. Hayes Inc. Nicotine replacement therapy for smoking cessation: nicotine patch. 2011. **APE2a**
45. Hayes Inc. Bupropion for smoking cessation. 2011. **APE2a**
46. Hayes Inc. Nicotine replacement therapy for smoking cessation: nicotine gum and nicotine lozenge. 2011. **APE2a**
47. Hayes Inc. Nicotine replacement therapy for smoking cessation: nicotine nasal spray and nicotine inhaler. 2011. **APE2a**
48. Heydari G, Masjedi M, Ahmady AE, et al. A comparative study on tobacco cessation methods: a quantitative systematic review. Int J Prev Med 2014 Jun;5(6):673-8. PMID: 25013685. **ABE2a, APE2a**
49. Hind D, Tappenden P, Peters J, et al. Varenicline in the management of smoking cessation: a single technology appraisal. Health Technology Assessment 2009;13((Suppl 2 Article 2)):9-13. PMID: none. **APE2a**
50. Hitsman B, Papandonatos GD, McChargue DE, et al. Past major depression and smoking cessation outcome: a systematic review and meta-analysis update. Addiction 2013 Feb;108(2):294-306. PMID: 23072580. **AME1**
51. Hoedjes M, Berks D, Vogel I, et al. Effect of postpartum lifestyle interventions on weight loss, smoking cessation, and prevention of smoking relapse: a systematic review. Obstetrical and Gynecological Survey 2010;65(10):631-52. PMID: 21182803. **PWBE11**
52. Hollands GJ, Vogt F, McDermott MÃ, et al. Interventions to increase adherence to medications for tobacco dependence. Cochrane Database of Systematic Reviews: Reviews 2011;Issue 6 PMID: none. **APE1**

53. Kaur K, Kaushal S, Chopra SC. Varenicline for smoking cessation: A review of the literature. Curr Ther Res Clin Exp 2009 Feb;70(1):35-54. **APE11**
54. Kimura K, Sairenchi T, Muto T. Meta-analysis study for one year effects of a nicotine patch. Journal of Health Science 2009;55(2):233-41. PMID: None. **APE11**
55. Kitikannakorn N, Chaiyakunapruk N, Nimpitakpong P, et al. An overview of the evidences of herbals for smoking cessation. Complementary Therapies in Medicine 2013;21(5):557-64. PMID: 24050594. **ABE7**
56. Lorencatto F, West R, Michie S. Specifying evidence-based behavior change techniques to aid smoking cessation in pregnancy. Nicotine Tob Res 2012 Sep;14(9):1019-26. PMID: 22318690. **PWBE2a**
57. Louik C, Kerr S, Mitchell AA. First-trimester exposure to bupropion and risk of cardiac malformations. Pharmacoepidemiol Drug Saf 2014 Jun 12;344:e1696. PMID: 24920293. **PPPE2**
58. Mantler T, Irwin JD, Morrow D. Motivational interviewing and smoking behaviors: a critical appraisal and literature review of selected cessation initiatives. Psychol Rep 2012 Apr;110(2):445-60. PMID: 22662398. **ABE11**
59. Manzoli L, La VC, Flacco ME, et al. Multicentric cohort study on the long-term efficacy and safety of electronic cigarettes: study design and methodology. BMC Public Health 2013;13:883. PMID: 24063569. **ENDSE2**
60. Mdege ND, Chindove SE-MA, Mdege NDnmacu. Effectiveness of tobacco use cessation interventions delivered by pharmacy personnel: A systematic review. [References]. Research in Social & Administrative Pharmacy 2014 Jan;10(1):21-44. PMID: 23743504. **ABE4, APE4, ACE4**
61. Mitchell, MD, Leone, F, Williams, K. Varenicline for smoking cessation. 2009. **APE11**
62. Napierkowski D. Acupuncture and related interventions for smoking cessation. International Journal of Evidence-Based Healthcare 2012;10(2):162-3. PMID: None. **ABE2a**
63. National Institute for Health and Care Excellence. Quitting smoking in pregnancy and following childbirth. London: National Institute for Health and Care Excellence; 2010. **PWCE2a**
64. Okoli CT, Torchalla I, Oliffe JL, et al. Men's smoking cessation interventions: a brief review. Journal of Men's Health 2011;8(2):100-8. PMID: None. **ACE11**
65. Oncken C. Nicotine replacement for smoking cessation during pregnancy. [References]. The New England Journal of Medicine 2012 Mar;366(9):846-7. PMID: 22375978. **PPPE2**
66. Polosa R, Caponnetto P, Morjaria JB, et al. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. BMC Public Health 2011;11:786. PMID: 21989407. **ENDSE2**
67. Polosa R, Morjaria JB, Caponnetto P, et al. Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. Intern Emerg Med 2013 Jul 20 PMID: 23873169. **ENDSE2**
68. Popova L, Ling PM. Alternative tobacco product use and smoking cessation: a national study. Am J Public Health 2013 May;103(5):923-30. PMID: 23488521. **ENDSE2**
69. Regan AK, Promoff G, Dube SR, et al. Electronic nicotine delivery systems: adult use and awareness of the 'e-cigarette' in the USA. Tob Control 2013 Jan;22(1):19-23. PMID: 22034071. **ENDSE2**
70. Rooke S, Thorsteinsson E, Karpin A, et al. Computer-delivered interventions for alcohol and tobacco use: a meta-analysis. Addiction 2010 Aug;105(8):1381-90. PMID: 20528806. **ABE6**
71. Rosen LJ, Noach MB, Winickoff JP, et al. Parental smoking cessation to protect young children: a systematic review and meta-analysis. Pediatrics 2012;129(1):141-52. PMID: 22201152. **ABE1, X2**
72. Rutqvist LE, Fry JS, Lee PN. Systematic review of Swedish snus for smoking cessation based on primary subject data from randomised clinical trials. Journal of Smoking Cessation 2013;8(1):33-44. PMID: none. **ABE4**
73. Saba M, Diep J, Saini B, et al. Meta-analysis of the effectiveness of smoking cessation interventions in community pharmacy. J Clin Pharm Ther 2014 Jun;39(3):240-7. PMID: 24749899. **ABE4**
74. Sanderson CL, Okuyemi K, Choi WS, et al. A review of tobacco use treatments in US ethnic minority populations. American Journal of Health Promotion 2011;25(5):S11-S30. PMID: 21510783. **ACE11**
75. Siegel MB, Tanwar KL, Wood KS. Electronic cigarettes as a smoking-cessation: tool results from an online survey. Am J Prev Med 2011 Apr;40(4):472-5. PMID: 21406283. **ENDSE2**

76. Song F, Huttunen-Lenz M, Holland R. Effectiveness of complex psycho-educational interventions for smoking relapse prevention: an exploratory meta-analysis. Journal of Public Health 2010;32(3):350-9. PMID: 19939787. **ABE4**
77. Spata J, Kelsberg G, Safranek S. Clinical inquiries. Does office spirometry improve quit rates in smokers? J Fam Pract 2010 Oct;59(10):593-4. PMID: 20922180. **ABE2a**
78. Spring B, Howe D, Berendsen M, et al. Behavioral intervention to promote smoking cessation and prevent weight gain: a systematic review and meta-analysis. Addiction 2009 Sep;104(9):1472-86. PMID: 19549058. **ABE1**
79. Steinberg MB, Zimmermann MH, Delnevo CD, et al. E-Cigarette Versus Nicotine Inhaler: Comparing the Perceptions and Experiences of Inhaled Nicotine Devices. J Gen Intern Med 2014 May 15 PMID: 24830741. **ENDSE6**
80. Suls JM, Luger TM, Curry SJ, et al. Efficacy of smoking-cessation interventions for young adults: a meta-analysis. Am J Prev Med 2012 Jun;42(6):655-62. PMID: 22608385. **ACE2a**
81. Tonstad S, Davies S, Flammer M, et al. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. Drug Saf 2010 Apr 1;33(4):289-301. PMID: 20297861. **APE2a**
82. Tsoi DT, Porwal M, Webster AC. Efficacy and safety of bupropion for smoking cessation and reduction in schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2010 May;196(5):346-53. PMID: 20435957. **AME10**
83. Umeda A, Kato T, Yamane T, et al. Does smoking cessation with varenicline worsen vascular endothelial function? BMJ Open 2013;3(6) PMID: 23794597. **APE2a**
84. Vaz LR, Leonardi BJ, Aveyard P, et al. Factors associated with smoking cessation in early and late pregnancy in the smoking, nicotine, and pregnancy trial: A trial of nicotine replacement therapy. Nicotine & Tobacco Research 2014;16(4):381-9. PMID: 24127265. **PPPE8**
85. Vickerman KA, Carpenter KM, Altman T, et al. Use of electronic cigarettes among state tobacco cessation quitline callers. Nicotine Tob Res 2013 Oct;15(10):1787-91. PMID: 23658395. **ENDSE2**
86. Webb MS, Rodriguez-Esquivel D, Baker EA. Smoking cessation interventions among Hispanics in the United States: A systematic review and mini meta-analysis. Am J Health Promot 2010 Nov;25(2):109-18. PMID: 21039291. **ACE7**
87. Weinberger AH, Mazure CM, Morlett A, et al. Two decades of smoking cessation treatment research on smokers with depression: 1990-2010. Nicotine Tob Res 2013 Jun;15(6):1014-31. PMID: 23100459. **AME6**
88. Weiner E, Ball MP, Buchholz AS, et al. Bupropion sustained release added to group support for smoking cessation in schizophrenia: a new randomized trial and a meta-analysis. J Clin Psychiatry 2012 Jan;73(1):95-102. PMID: 21535998. **AME2a**
89. Wray JM, Gass JC, Tiffany ST. A systematic review of the relationships between craving and smoking cessation. Nicotine Tob Res 2013 Jul;15(7):1167-82. PMID: 23291636. **ACE6**

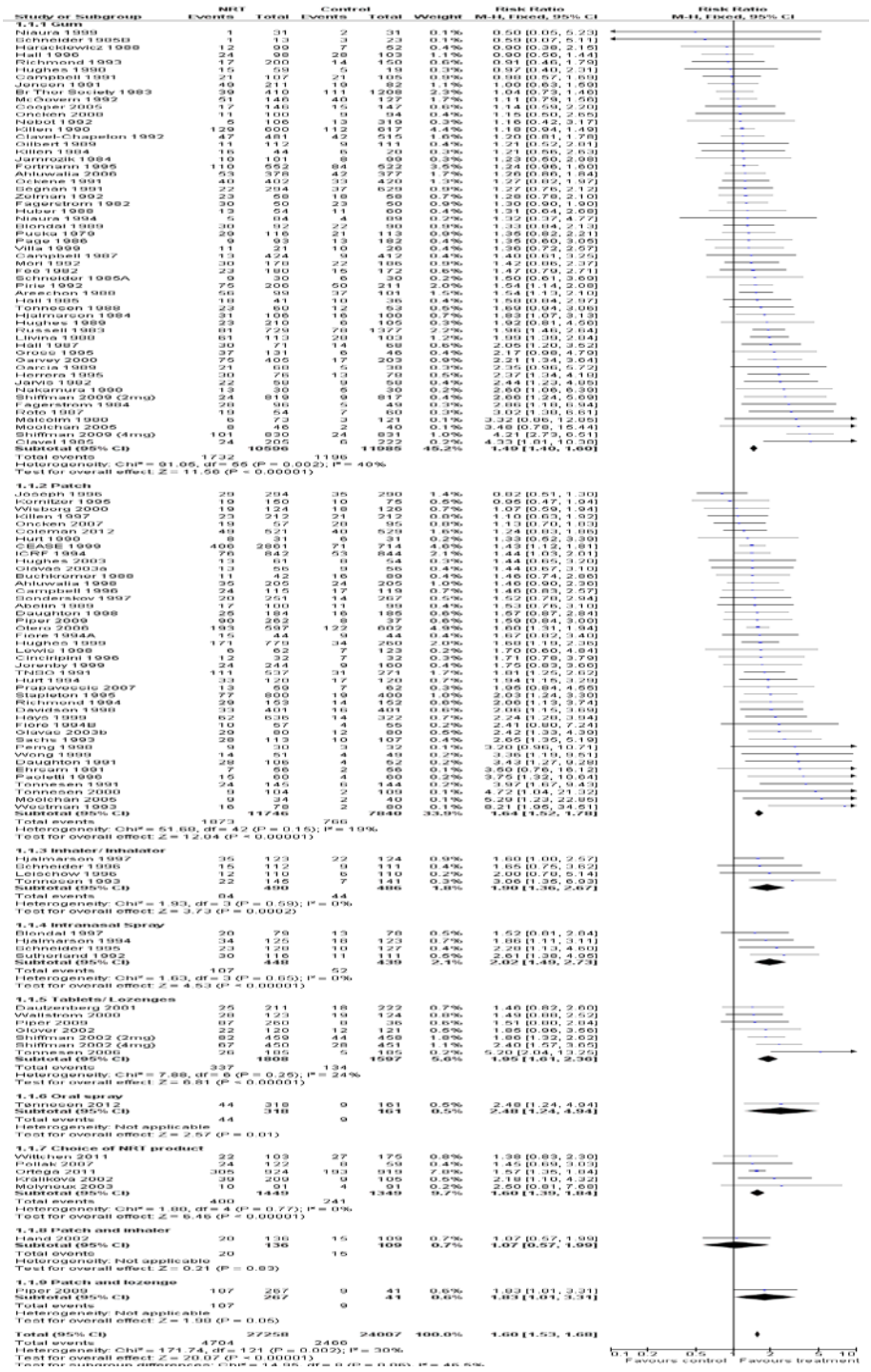
Appendix E. Poor-Quality Existing Systematic Reviews

Review	Reasons for Poor Quality Rating
Ferron 2009	• Dual study selection and dual data extraction not reported • Number of studies screened and excluded not reported • List of excluded studies not provided • Quality assessment of individual studies not performed or documented • Included single-group studies and calculated effect sizes based on post-measurements only • Potential conflicts of interest/source(s) of support of the systematic review not reported
Hoedjes 2010	• Inclusion criteria changed *post hoc* after no evidence was found related to the *a priori* study aims • Literature search terms and supplemental searches not reported • Dual study selection and dual data extraction not reported • List of excluded studies not provided • Quality assessment of individual studies not performed or documented; no discussion of limitations in the body of evidence in the discussion • Intervention for this review was ill-defined with "lifestyle interventions" broadly considered across a range of topics for postpartum women
Kaur 2009	• Dual study selection and dual data extraction not reported • Supplemental searches not reported • List of excluded studies not provided • Quality assessment of individual studies not performed or documented; no discussion of limitations in the body of evidence in the discussion • Potential conflicts of interest/source(s) of support of the included studies and systematic review not reported
Kimura 2009	• Comprehensive literature search not performed (i.e., search dates not reported, only 1 search database; supplemental searches not reported) • Dual study selection and dual data extraction not reported • List of excluded studies not provided • Methods state, “The number of subjects in the selected literature markedly differed; we cannot simply review these data.” Not clear what implications this had on the results. • Minimal detail provided on included studies • Quality assessment of individual studies not performed or documented; no discussion of limitations in the body of evidence in the discussion • Potential conflicts of interest/source(s) of support of the included studies and systematic review not reported
Mantler 2012	• Literature search dates and search terms not reported • Dual study selection and dual data extraction not reported • Number of studies screened and excluded not reported • List of excluded studies not provided • Quality of individual studies assessed but overall quality and individual quality domains are not reported for each included study • No discussion on lack of quantitative pooling • Potential conflicts of interest/source(s) of support of the systematic review not reported
Mitchell 2009	• Literature search terms not reported • Dual study selection and dual data extraction not reported • Number of studies screened and excluded not reported • List of excluded studies not provided • Limited description of included studies • Quality of individual studies assessed but not documented or used appropriately in formulating conclusions • Heterogeneity of studies not accounted for in meta-analysis • Likelihood of publication bias not assessed • Potential conflicts of interest/source(s) of support of the systematic review not reported

Appendix E. Poor-Quality Existing Systematic Reviews

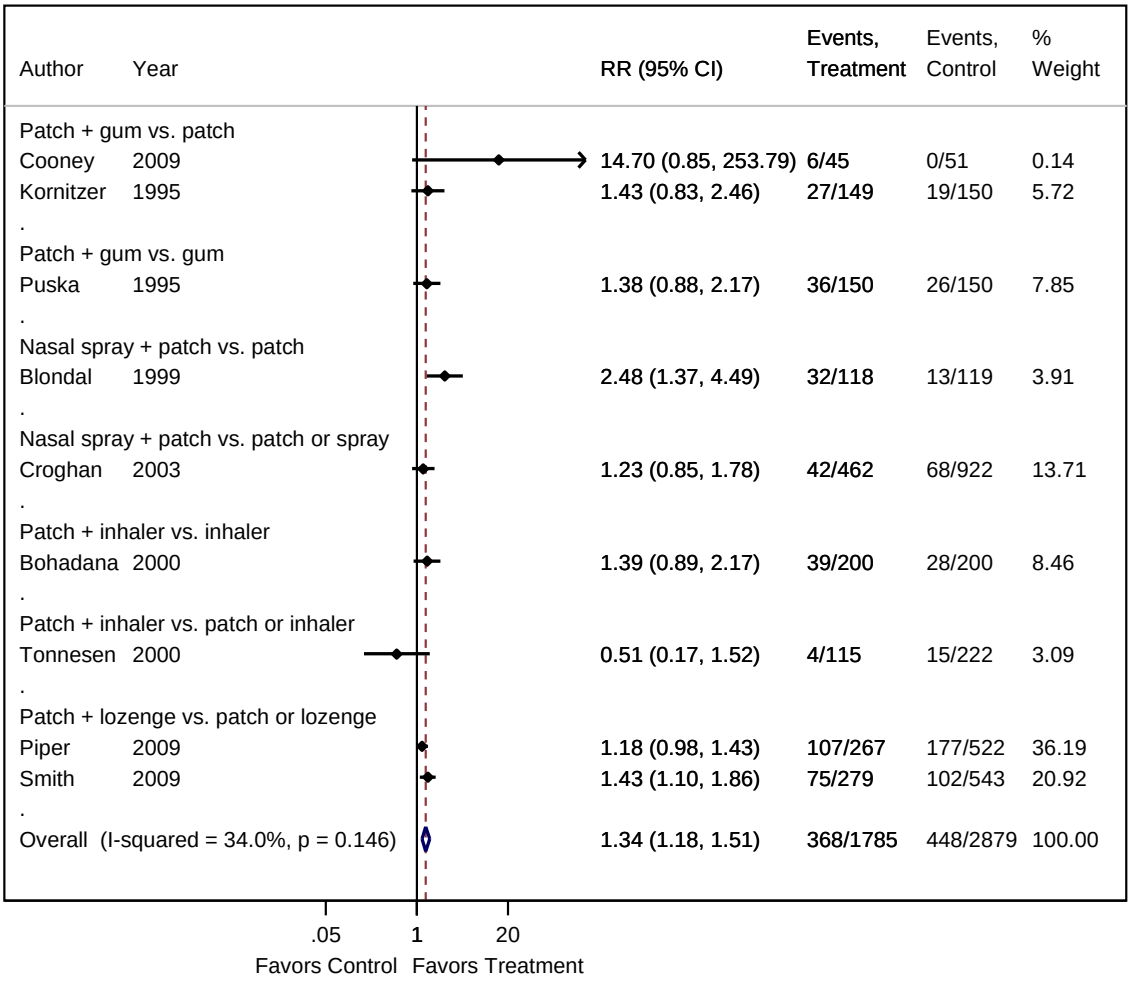
Review	Reasons for Poor Quality Rating
Okoli 2011	• Aim is to evaluate the efficacy of interventions among men, but included studies did not emphasize sex as a key factor in design or delivery of interventions • Dual study selection and dual data extraction not reported • Number of studies screened and excluded not reported • List of excluded studies not provided • Quality assessment of individual studies not performed or documented; no discussion of limitations in the body of evidence in the discussion • Potential conflicts of interest/source(s) of support of the included studies not reported
Sanderson 2011	• Not all included studies addressed the primary research question (i.e., purpose was to review interventions among ethnic and minority smokers, yet required that only 10% of the sample were ethnic or minority participants) • List of a number of literature search databases but state that MEDLINE was the “primary” source of literature. Not clear how that impacted the results of the search process. • Dual study selection not reported • Number of studies screened and excluded not reported • List of excluded studies not provided • Quality assessment of individual studies not performed or documented; no discussion of limitations in the body of evidence in the discussion • Potential conflicts of interest/source(s) of support of the included studies not reported

Appendix F Figure 1. Any Type of NRT vs. Placebo/No NRT Control: Smoking Abstinence at 6+ Months Followup (Stead, 2012a)[140]

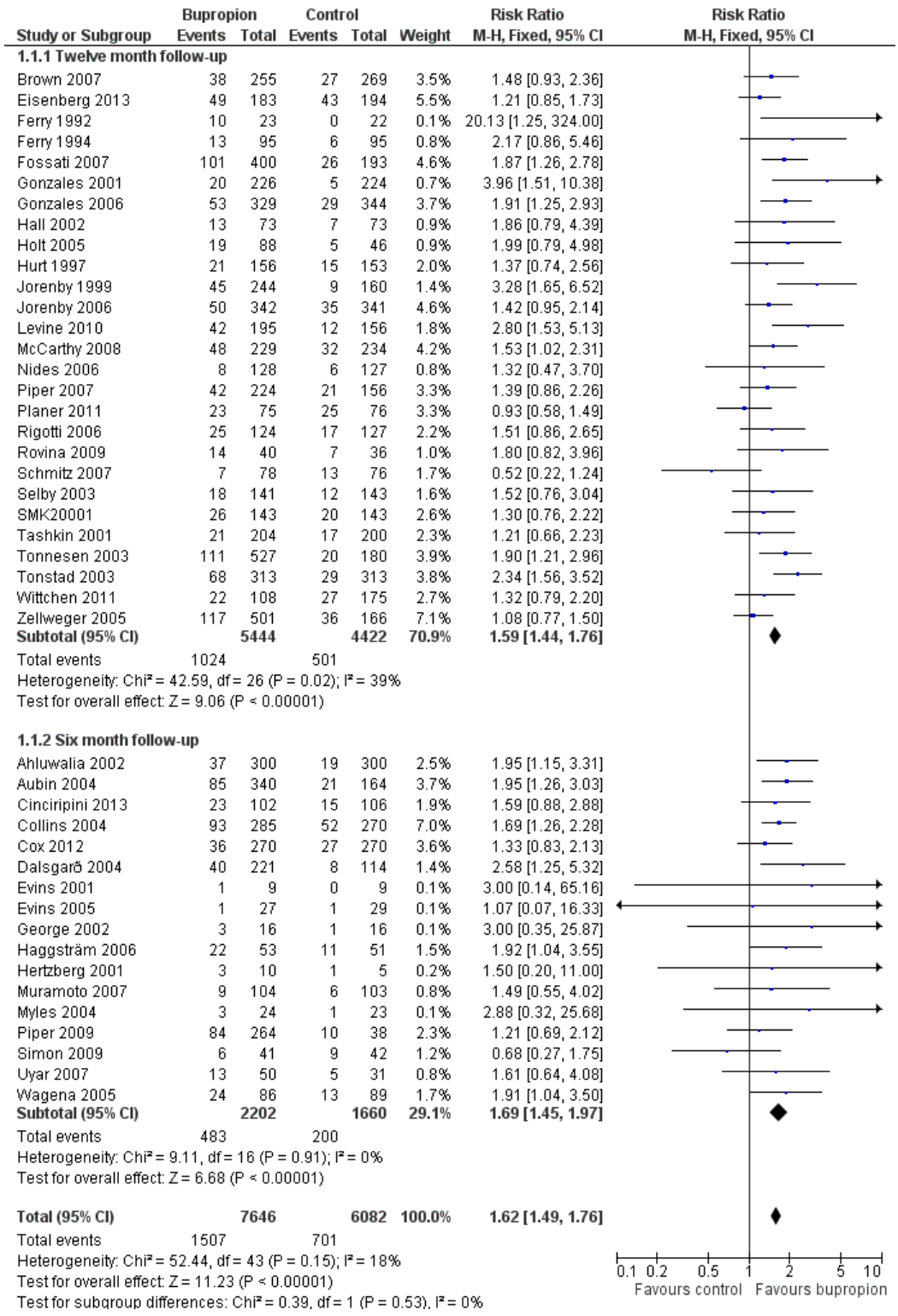


Source: Stead LF. Nicotine replacement therapy for smoking cessation (Review). Cochrane Database of Systematic Reviews 2012, Issue 11. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 2. Combinations of Different Types of NRT vs. Single Type: Smoking Abstinence at 6+ Months Followup (Stead, 2012a)[140]

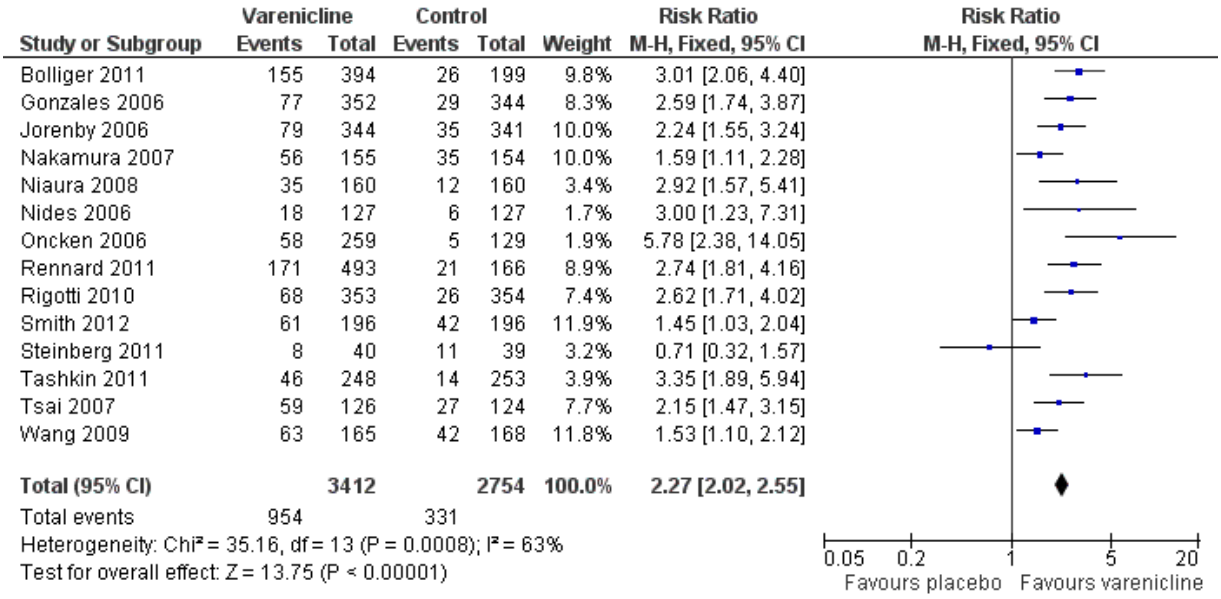


Appendix F Figure 3. Bupropion vs. Placebo/Control: Smoking Abstinence at 6+ Months Followup (Hughes, 2014)[121]



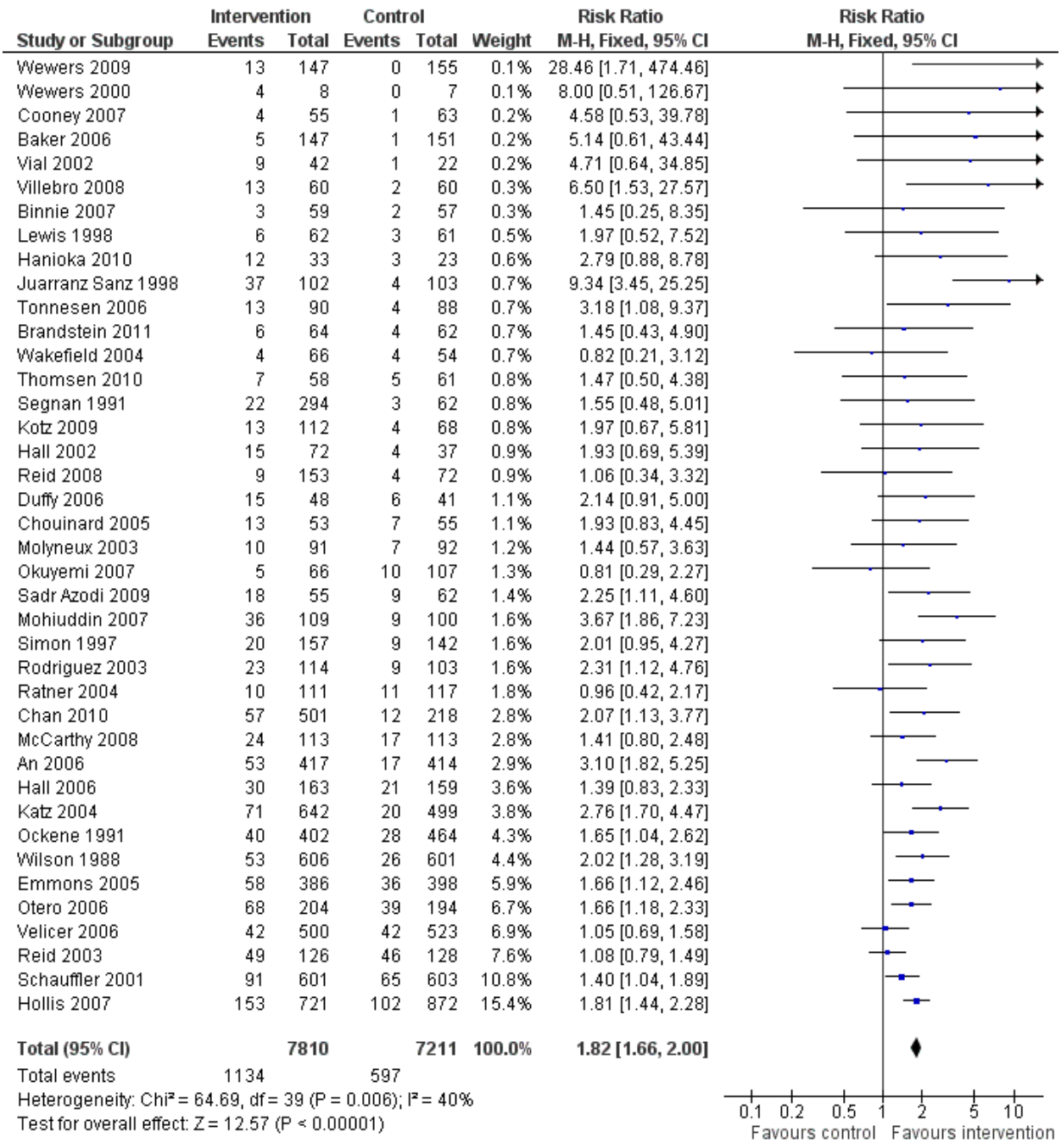
Source: Hughes JR. Antidepressants for smoking cessation (Review). Cochrane Database of Systematic Reviews 2014, Issue 1. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 4. Varenicline vs. Placebo: Continuous Abstinence at Longest Followup (Cahill, 2012)[154]



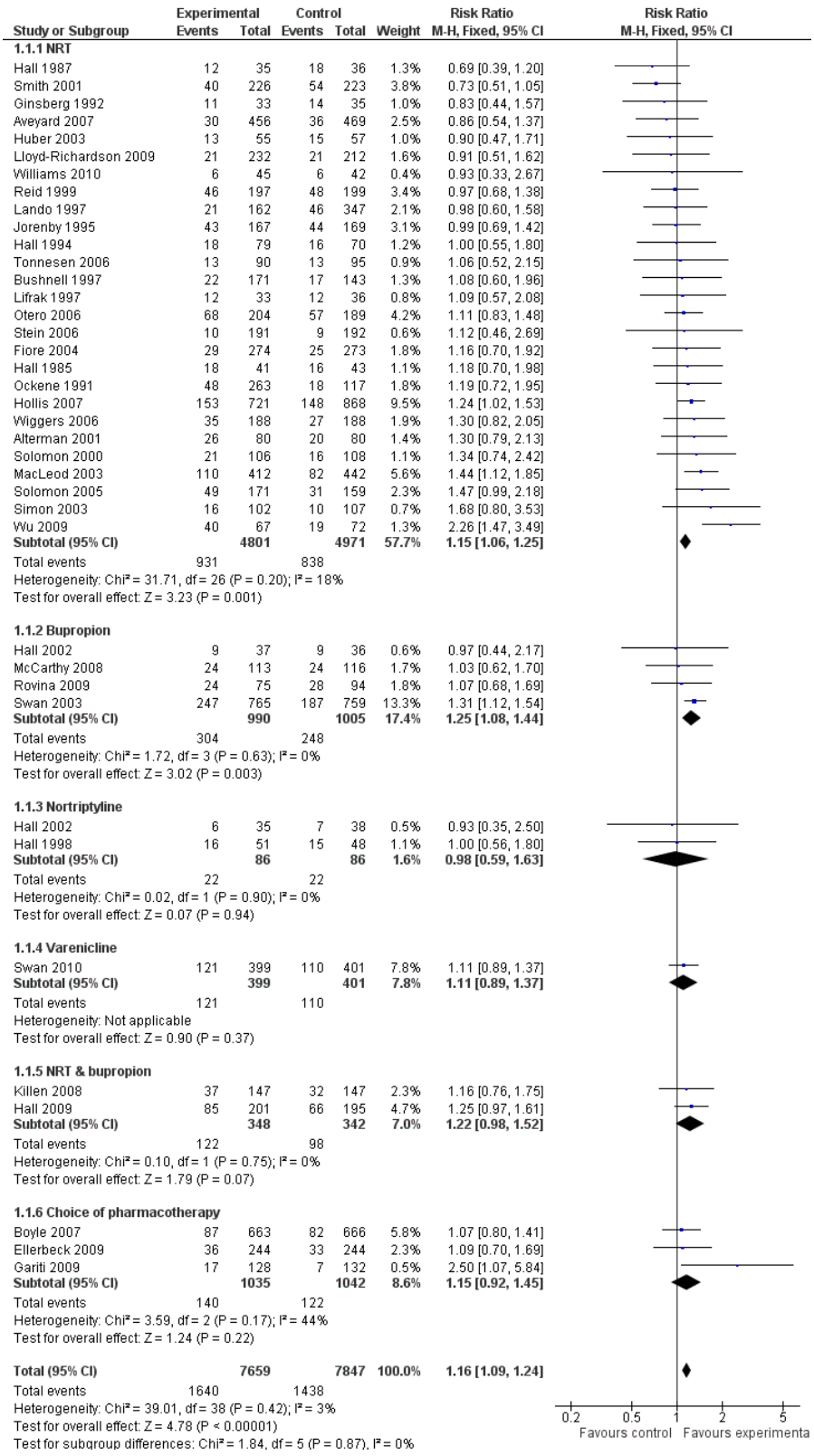
Source: Cahill K. Nicotine receptor partial agonists for smoking cessation (Review). Cochrane Database of Systematic Reviews 2012, Issue 4. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 5. Combined Intervention vs. Control: Smoking Abstinence at Longest Followup (Stead 2012b)[138]



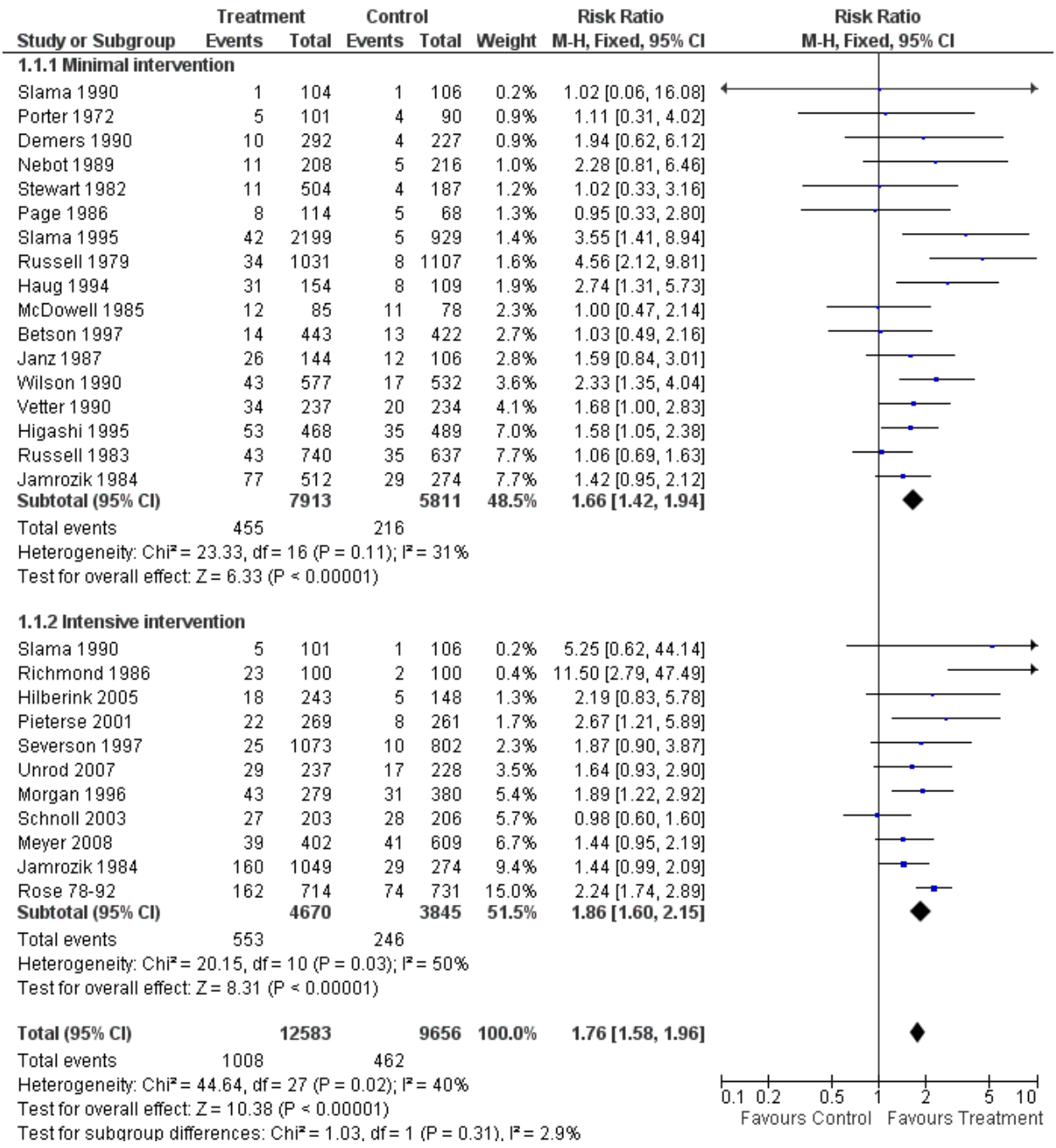
Source: Stead LF. Combined pharmacotherapy and behavioral interventions for smoking cessation (Review). Cochrane Database of Systematic Reviews 2012, Issue 12. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 6. Effect of Increasing Behavioral Support: Smoking Abstinence at Longest Followup (Stead, 2013a)[142]



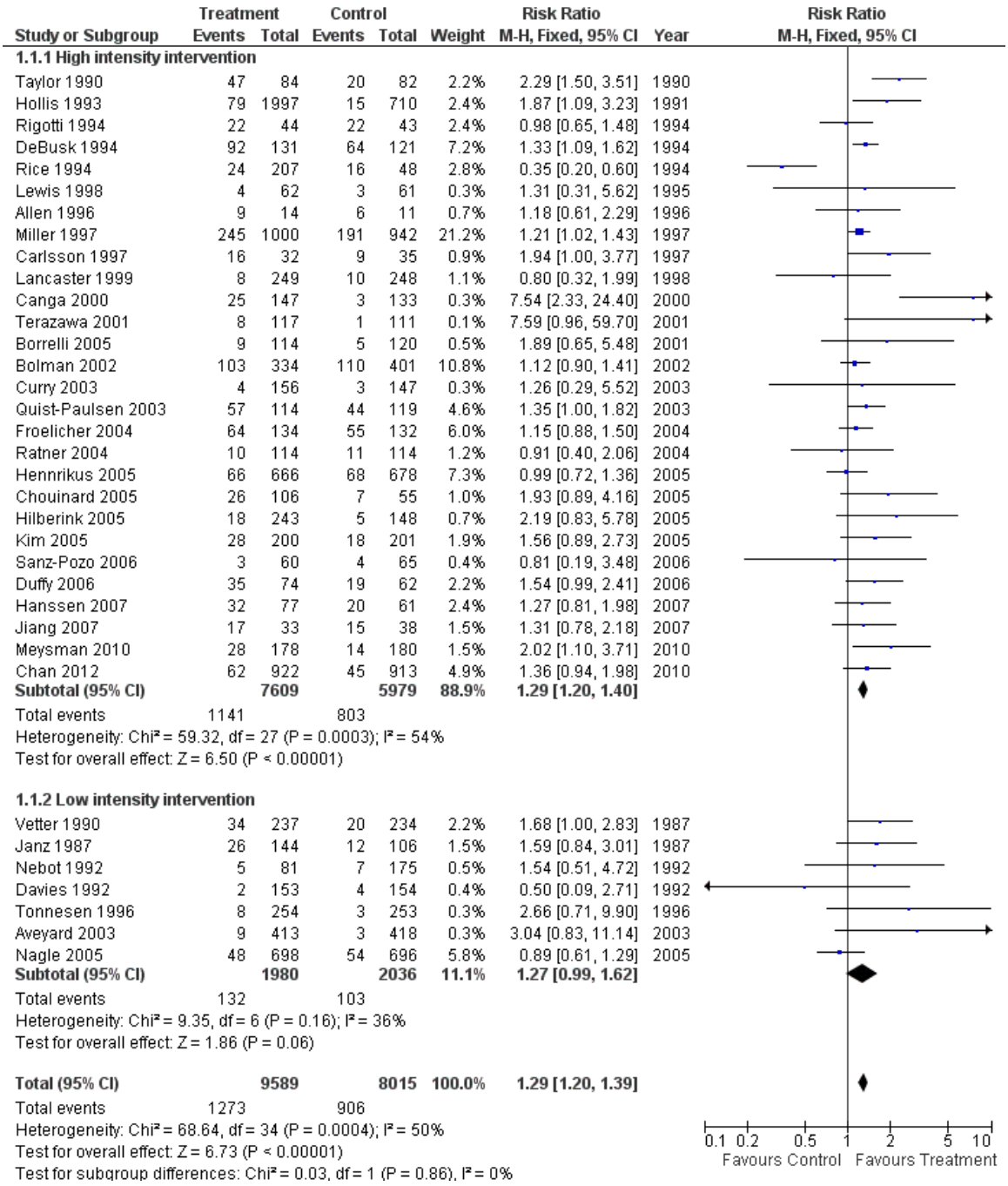
Source: Stead LF. Behavioral interventions as adjuncts to pharmacotherapy for smoking cessation (Review). Cochrane Database of Systematic Reviews 2013, Issue 3. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 7. Effect of Advice vs. Control (by Intensity): Smoking Abstinence at Longest Followup (Stead, 2013b)[139]



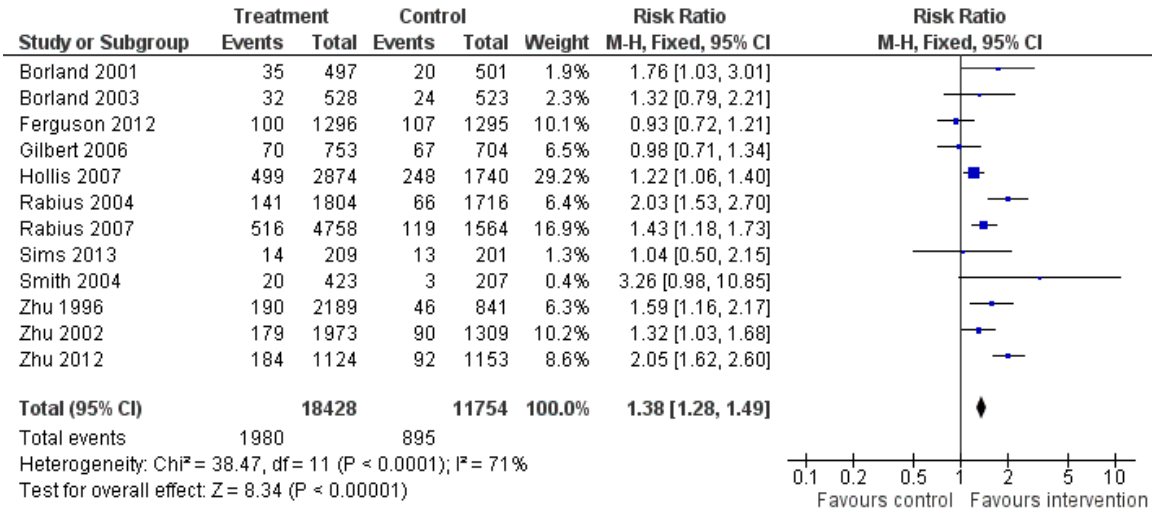
Source: Stead LF. Physician advice for smoking cessation (Review). Cochrane Database of Systematic Reviews 2013, Issue 5. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 8. Nursing Interventions vs. Control (by Intensity of Intervention): Smoking Abstinence at Longest Followup (Rice, 2013)[136]



Source: Rice VH. Nursing interventions for smoking cessation (Review). Cochrane Database of Systematic Reviews 2013, Issue 8. *Permission to reprint this figure granted by John Wiley and Sons.*

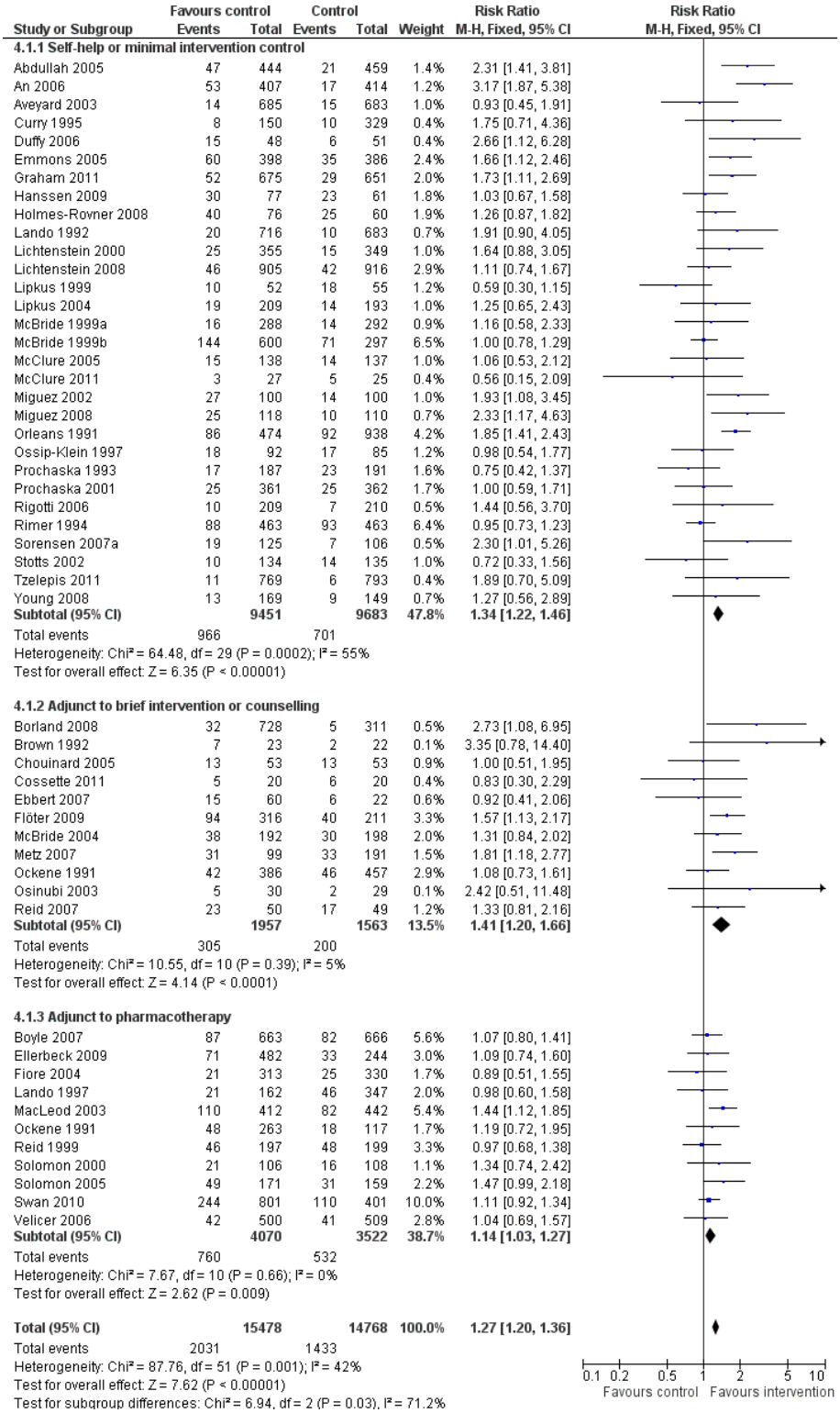
Appendix F Figure 9. Interventions for Callers to Quitlines*: Smoking Abstinence at Longest Followup (Stead 2013c)[141]



***** Pooled results based on fixed vs. random effects model.

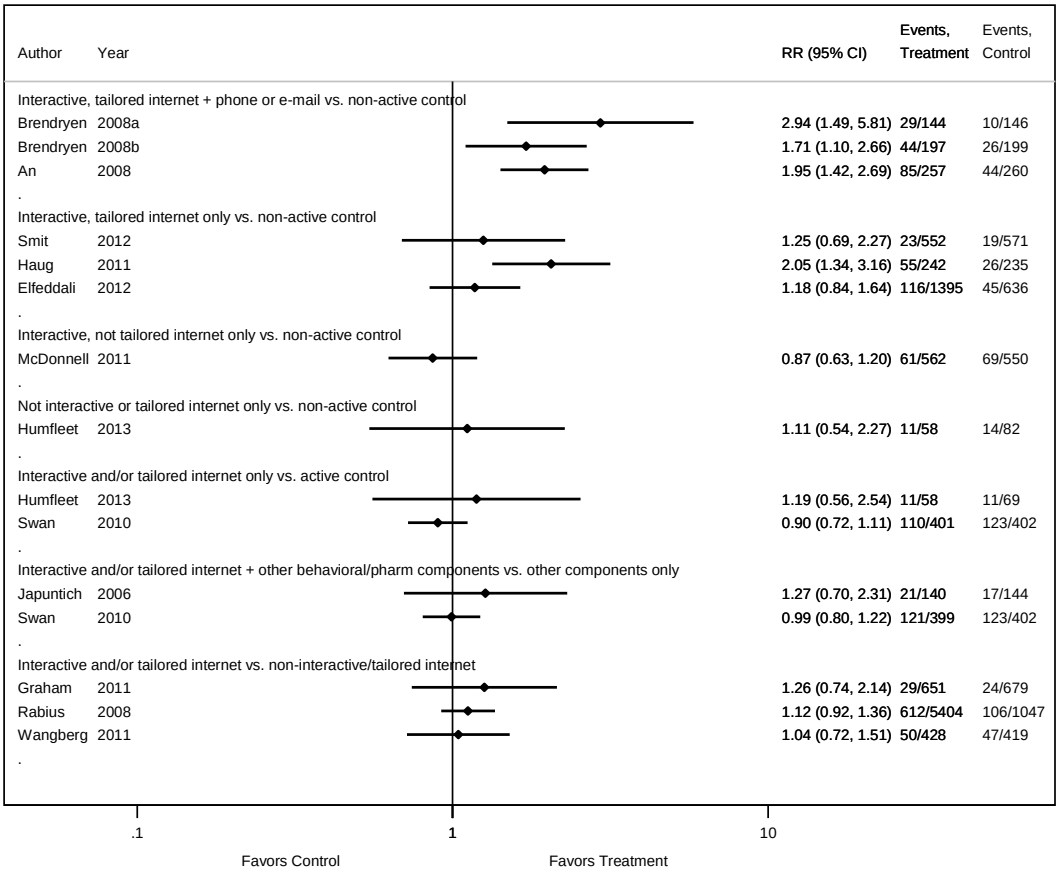
Source: Stead LF. Telephone counseling for smoking cessation (Review). Cochrane Database of Systematic Reviews 2013, Issue 8. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 10. Interventions for Smokers Not Calling Quitlines (by Baseline Support): Smoking Abstinence at Longest Followup (Stead 2013c)[141]



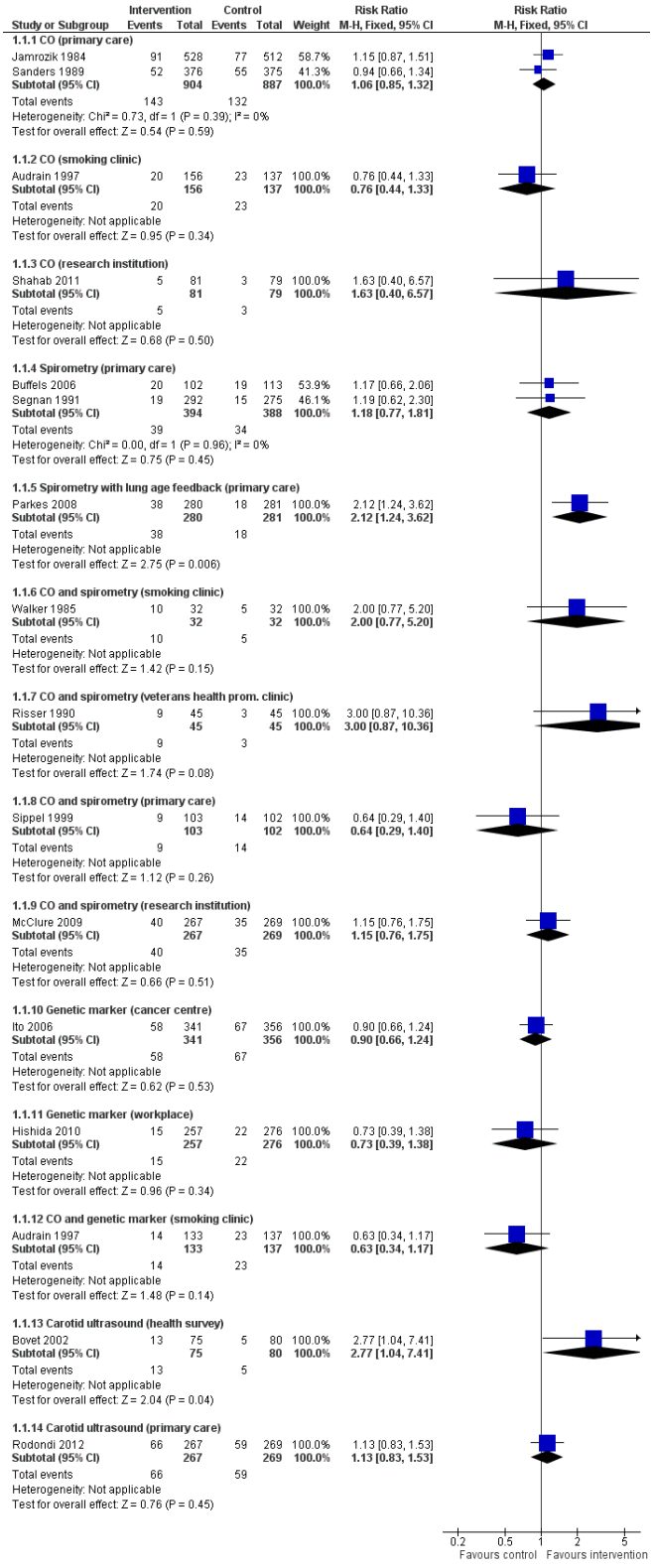
Source: Stead LF. Telephone counseling for smoking cessation (Review). Cochrane Database of Systematic Reviews 2013, Issue 8. *Permission to reprint this figure granted by John Wiley and Sons.*

Appendix F Figure 11. Internet-Based Interventions (by Type of Intervention and Control): Smoking Abstinence at Longest Followup (Civljak, 2013)[113]



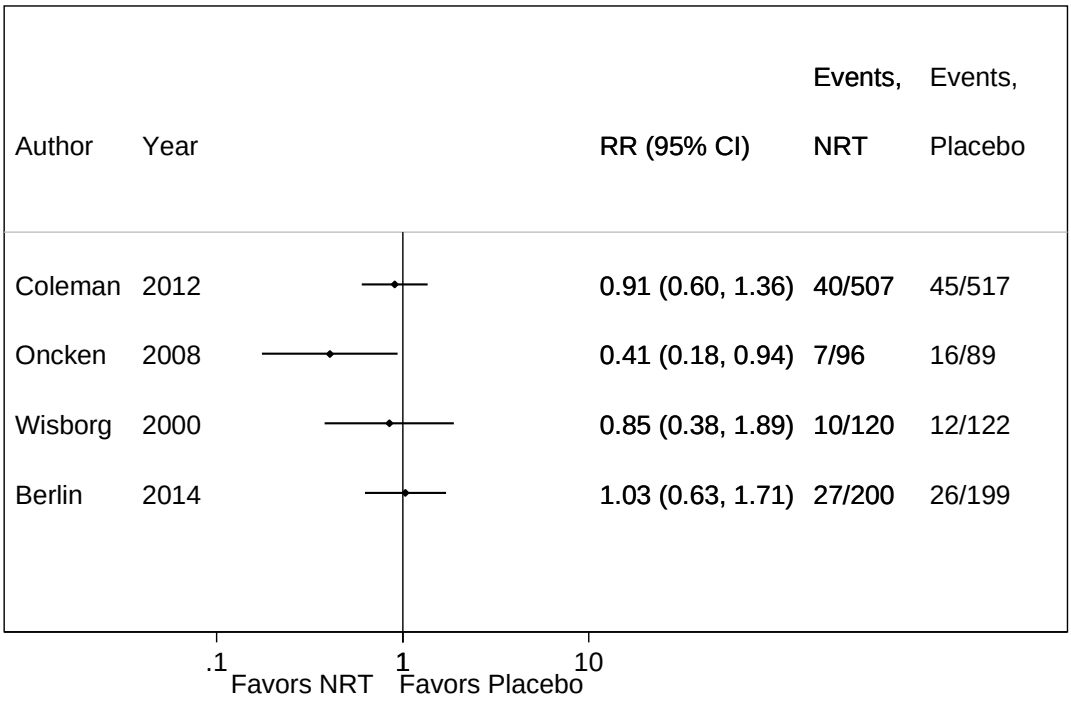
Source: Civljak M. Internet-based interventions for smoking cessation (Review). Cochrane Database of Systematic Reviews 2013, Issue 7. *Permission to reprint this figure granted by John Wiley and Sons*

Appendix F Figure 12. Smoking Cessation for All Intervention Comparisons (Bize 2012)[102]

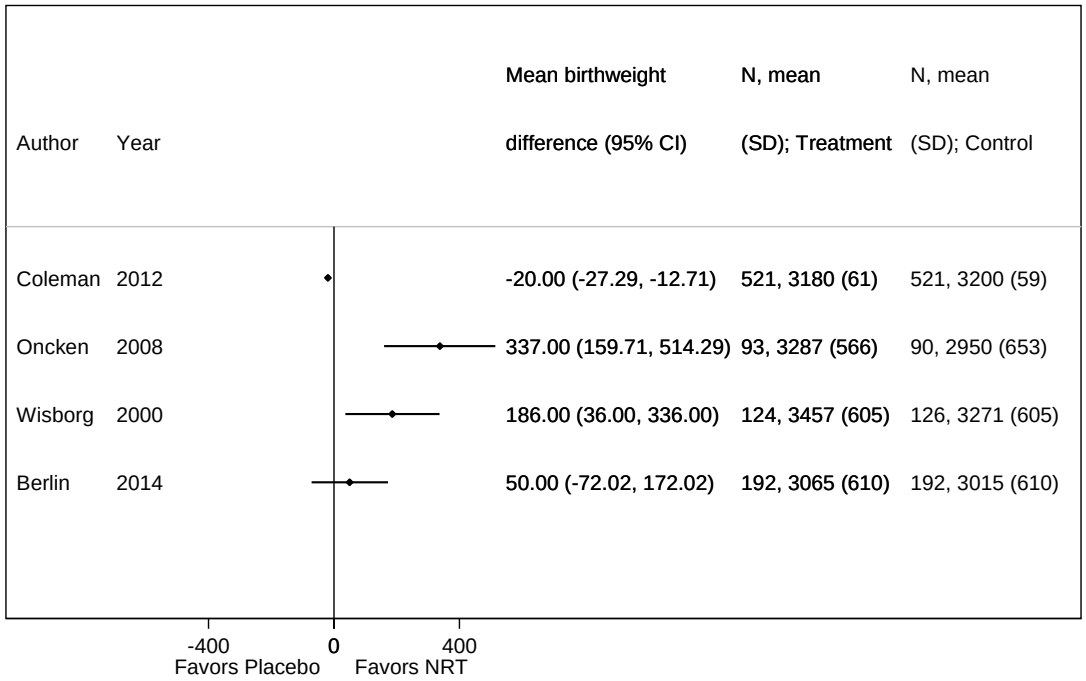


Source: Bize R. Biomedical risk assessment as an aid for smoking cessation (Review). Cochrane Database of Systematic Reviews 2012, Issue 12. *Permission to reprint this figure granted by John Wiley and Sons.*

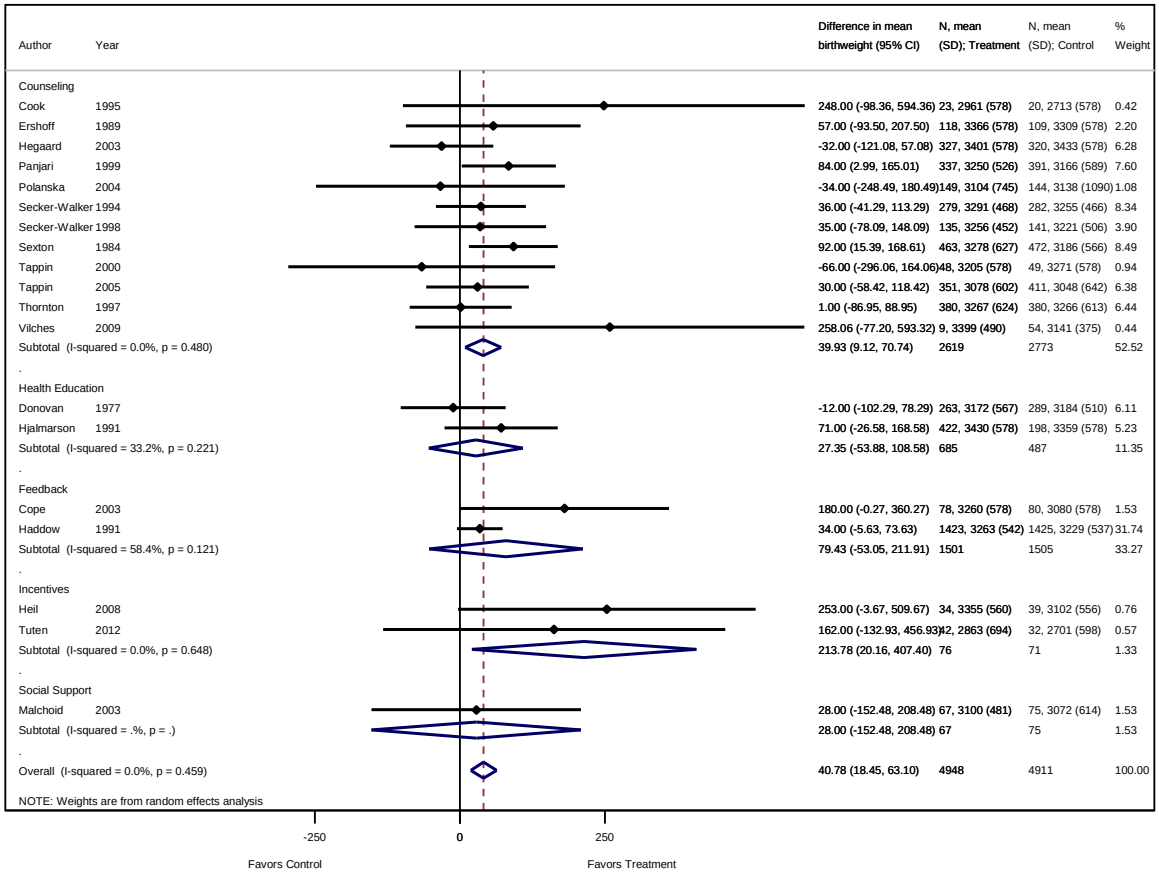
Appendix F Figure 13. NRT Interventions for Smoking Cessation During Pregnancy, Preterm Birth at <37 Weeks (Coleman 2012 + Study Identified in Bridge Search)[92,101]



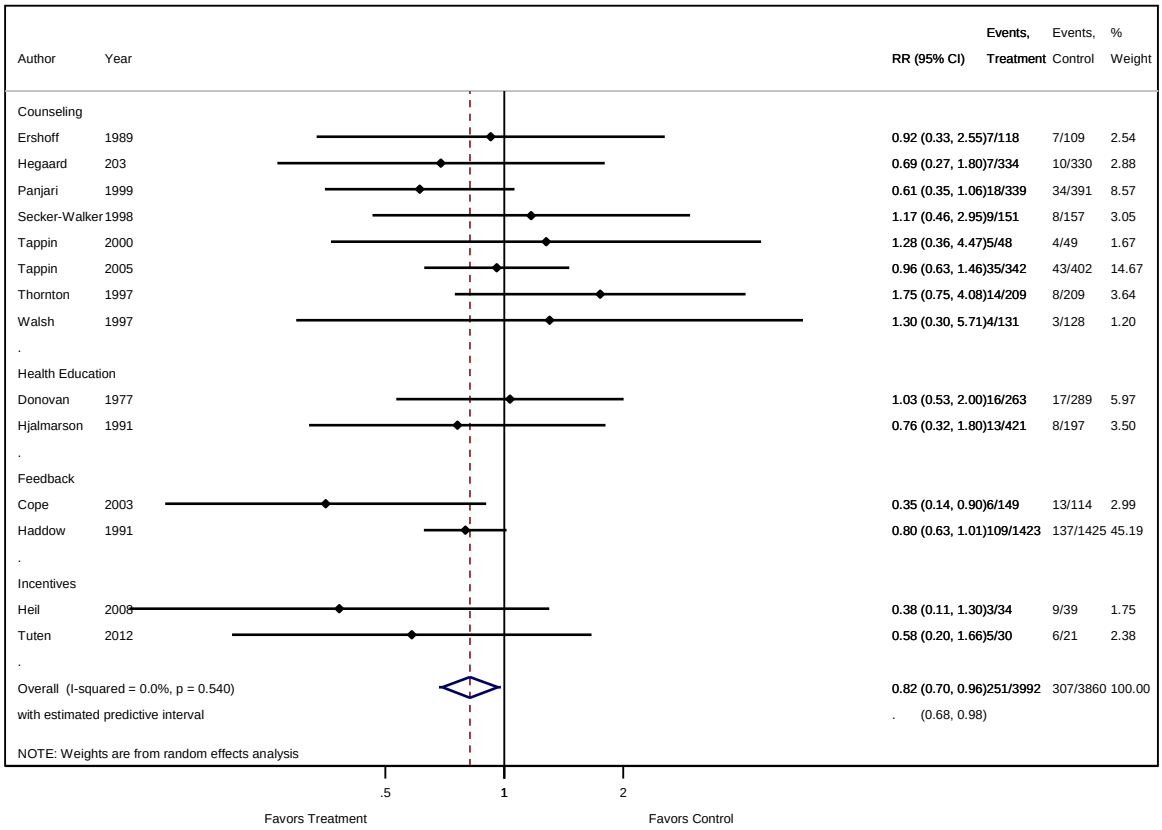
Appendix F Figure 14. NRT Interventions for Smoking Cessation During Pregnancy, Mean Birth Weight in Grams (Coleman 2012 + Study Identified in Bridge Search)[92,101]



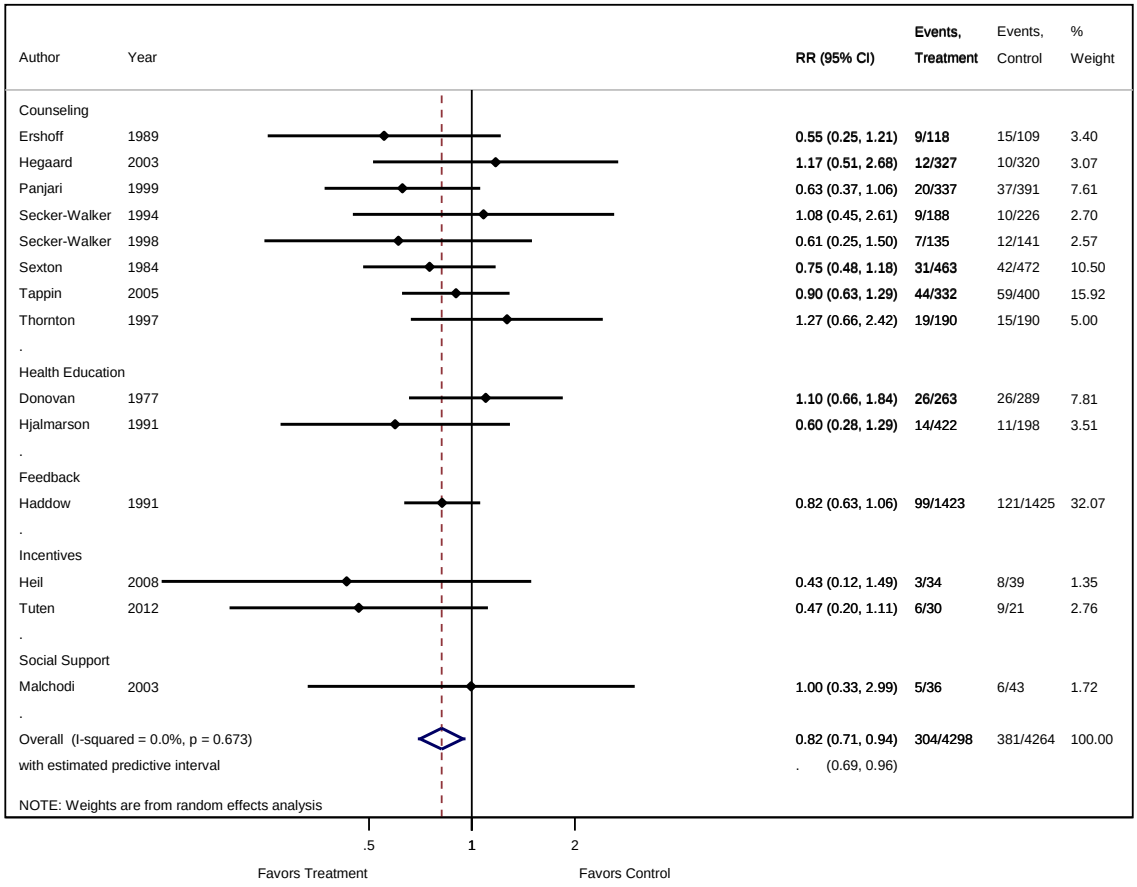
Appendix F Figure 15. Behavioral Interventions for Smoking Cessation During Pregnancy, Mean Birth Weight in Grams (Chamberlain, 2013)[110]



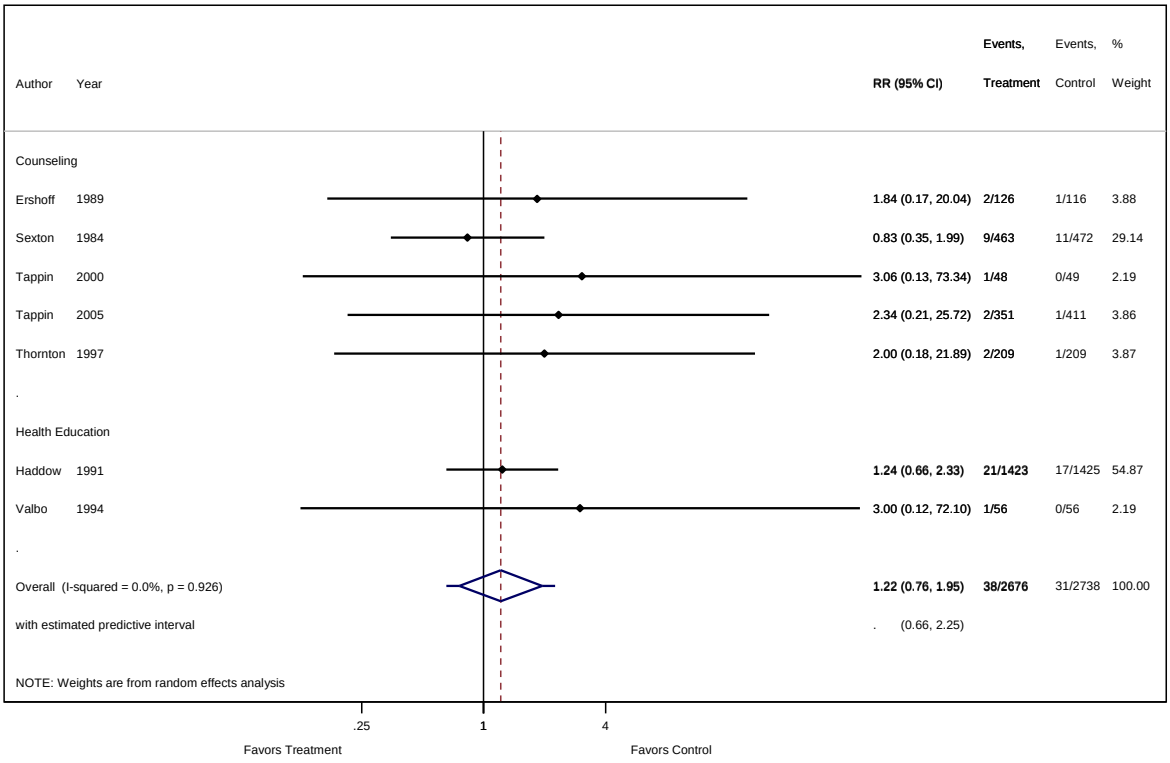
Appendix F Figure 16. Behavioral Interventions for Smoking Cessation During Pregnancy, Preterm Birth (<37 Weeks Gestation) (Chamberlain, 2013)[110]



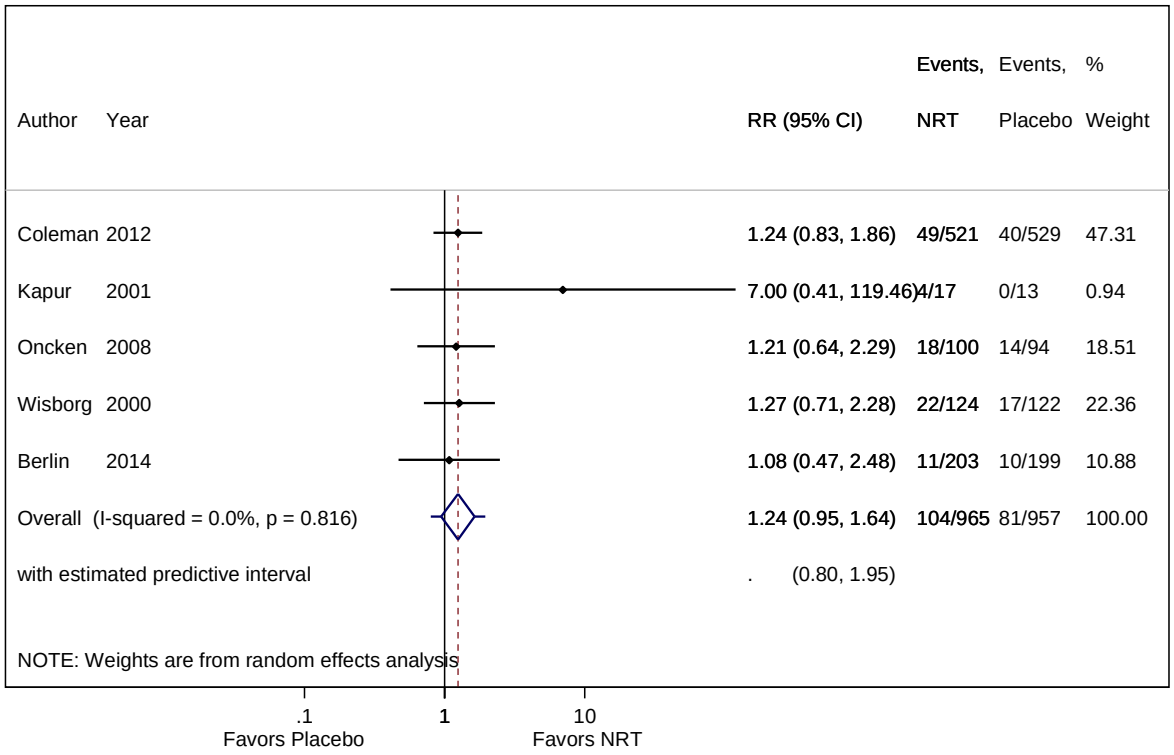
Appendix F Figure 17. Behavioral Interventions for Smoking Cessation During Pregnancy, Low Birth Weight (<2500 g) (Chamberlain, 2013)[110]



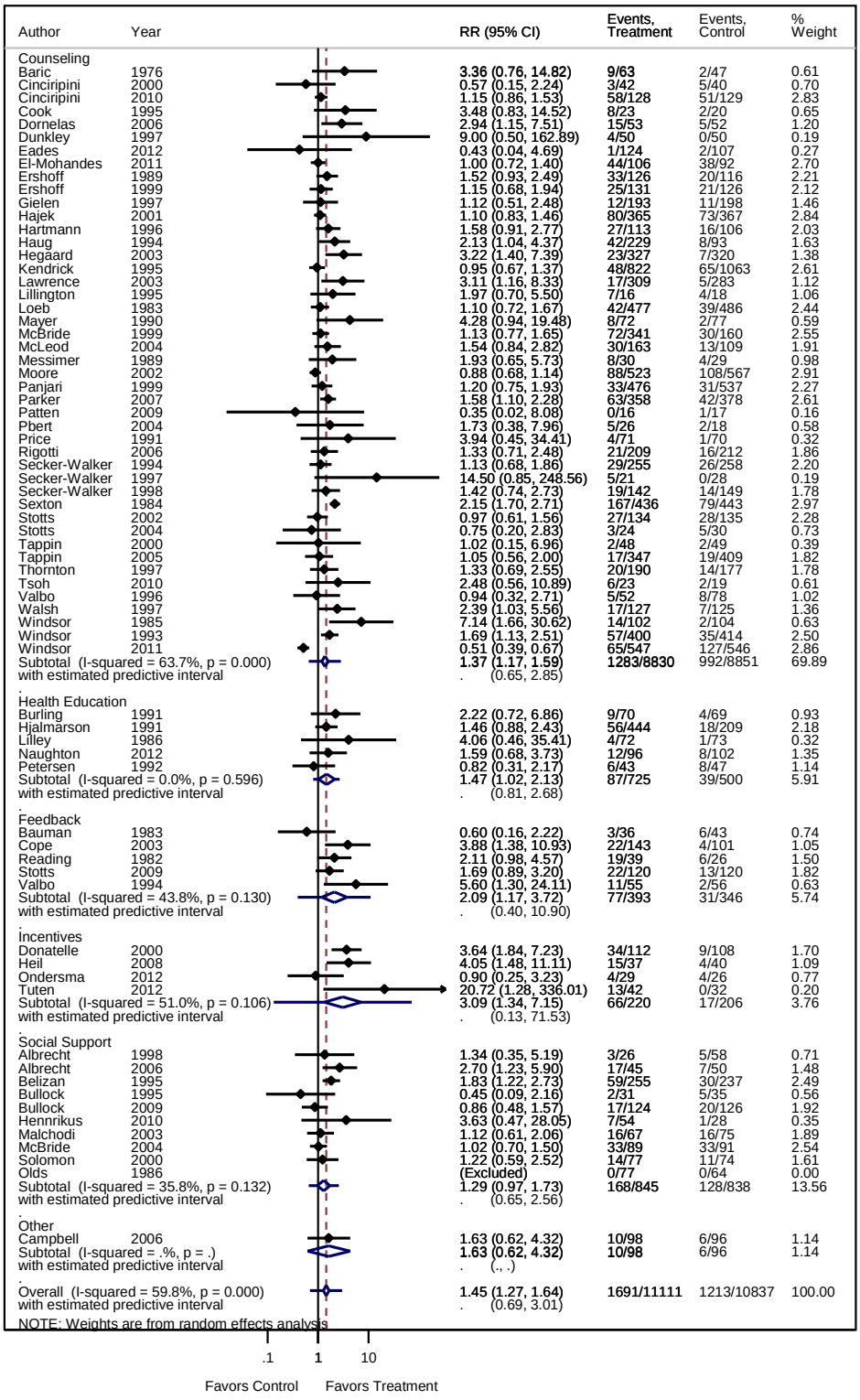
Appendix F Figure 18. Behavioral Interventions for Smoking Cessation During Pregnancy, Stillbirth (Chamberlain, 2013)[110]



Appendix F Figure 19. NRT Use in Pregnant Women, Validated Smoking Cessation in Later Pregnancy (Coleman 2012 + Study Identified in Bridge Search)[92,101]



Appendix F Figure 20. Behavioral Interventions for Smoking Cessation During Pregnancy, Smoking Cessation in Late Pregnancy (Chamberlain, 2013)[110]



Appendix G Table 1. Ongoing or Recently Completed Studies: Pharmacotherapy in Pregnant Women

Study, Year Initiated CT Identifier	Design	Aim	Location	Number of participants	Intervention description	Relevant outcomes	Current status
El-Mohandes, 2006 NCT00341432	RCT	To compare the effectiveness of counseling plus use of a nicotine patch with counseling alone for helping pregnant women quit smoking	United States	Estimated enrollment: 300	Counseling plus the nicotine patch vs. counseling alone	Smoking abstinence	Completed April 2011
GlaxoSmithKline, 2012 NCT01597661	Retrospective case control	To investigate the link between exposure to buproprion in the 1st trimester and resulting cardiac birth defects using data from the Slone Epidemiology Center Birth Defects Study.	United States	Estimated enrollment: NR	Exposure to buproprion during the 1st trimester vs. no exposure	Cardiac birth defects	Completed August 2012
Koren, 2008 NCT00744913	RCT	To assess the effectiveness of NRT plus counselling treatment in aiding smoking cessation among pregnant women.	United States	Estimated enrollment: NR	Nicoderm patch (14 mg/day or 21 mg/day) plus counseling vs. counseling alone.	Smoking abstinence	Withdrawn
Myers, 2003 NCT00224419	RCT	to evaluate the effectiveness of providing over-the-counter NRT, choice of gum, lozenge or patch to promote prepartum smoking cessation.	United States	Estimated enrollment: 181	Cognitive behavioral counseling plus NRT (patch [14 or 21 mg], lozenge [2 mg], or gum [2 mg]) vs. counseling alone.	Smoking abstinence	Terminated
Nanovskaya, 2011 NCT01390246	RCT	To evaluate the preliminary safety and efficacy of bupropion in combination with behavioral counseling for smoking cessation during pregnancy.	United States	Estimated enrollment: 150	Bupropion (150 mg twice a day) for 12 weeks plus behavioral counseling (35 min counseling sessions at each of the first 2 visits and 10 minutes at subsequent visits) vs. placebo plus the same behavioral counseling schedule	Smoking abstinence; adverse effects; perinatal/ neonatal outcomes	Recruiting Estimated completion: April 2015
Oncken, 2002 NCT00115687	RCT	To evaluate the safety and effectiveness of 2 mg nicotine gum in promoting smoking cessation during pregnancy	United States	Estimated enrollment: 250	Nicotine gum (2 mg) vs. placebo	Smoking abstinence; adverse effects; perinatal/ neonatal outcomes	Terminated

Appendix G Table 1. Ongoing or Recently Completed Studies: Pharmacotherapy in Pregnant Women

Study, Year Initiated CT Identifier	Design	Aim	Location	Number of participants	Intervention description	Relevant outcomes	Current status
Oncken, 2010 NCT01656733	RCT	To evaluate the effectiveness of the nicotine inhaler in combination with counseling in helping pregnant women quit smoking.	United States	Estimated enrollment: 360	Nicotrol Inhaler (1-12 cartridges per day), for 6 weeks plus behavioral counseling vs. a placebo inhaler plus behavioral counseling.	Smoking abstinence; adverse effects; perinatal/ neonatal outcomes	Recruiting Estimated completion: November 2015
Placebo-controlled Trial of Bupropion for Smoking Cessation in Pregnant Women (BIBS), 2014 NCT02188459	RCT	To evaluate the efficacy of bupropion in assisting pregnant smokers to quit smoking.	United States	Estimated enrollment: 360	Bupropion (300 mg/day) vs. placebo	Smoking abstinence; adverse effects; perinatal/ neonatal outcomes	Not yet recruiting Estimated completion: January 2020
Study of Nicotine Patch in Pregnancy (SNIPP), 2007 NCT00507975	RCT	To assess the effectiveness of the nicotine patch comparatively to a placebo patch in pregnant women on birth weight and maternal smoking abstinence.	France	Estimated enrollment: 404	Nicotine patch (dose NR) vs. placebo	Smoking abstinence; adverse effects; perinatal/ neonatal outcomes	Completed November 2012
Stotts, 2011 NCT01286402	RCT	To gather preliminary effectiveness and safety data on the use of bupropion for smoking cessation in pregnant women attending a community prenatal clinic.	United States	Estimated enrollment: 50	Buproprion (150 mg/day for the 1st 3 days; 300 mg/day for the remainder of the 8 weeks) vs. placebo	Smoking abstinence; adverse effects; perinatal/ neonatal outcomes	Ongoing, not recruiting Estimated completion: April 2014
Varenicline Pregnancy Cohort Study, 2007 NCT01290445	Prospective cohort	To examine whether varenicline use during pregnancy is associated with an increased risk of major congenital malformations in infants above that associated with smoking during pregnancy.	Denmark and Sweden	Estimated enrollment: 904,585	Infants exposed in utero to varenicline vs. infants exposed to cigarette smoke in utero vs. infants not exposed to varenicline or cigarette smoke in utero	Prevalence of major congenital malformation, prevalence of other perinatal/ neonatal outcomes	Enrolling by invitation

Appendix G Table 2. Ongoing or Recently Completed Studies: Electronic Nicotine Delivery Systems (ENDS)

Study, Year initiated	Identifier Principal Investigator	Design	Aim	Location	Number of participants	Intervention description	Relevant outcomes	Current status
High Cessation Rates in Smokers Using Personal Vaporizers (VAPECIG)	NCT02124200 (ClinicalTrials.gov) Riccardo Polosa (University degli Studi di Catania)	Prospective 6-month pilot study	To evaluate changes in smoking habits of regular smokers unwilling to quit who were asked to switch to a second generation device focusing on smoking reduction and smoking abstinence	Italy	Estimated enrollment: 40	Electronic cigarette (eGo CE4 9 mg nicotine)	Sustained 50% reduction in the number of cigarette/day at week 24 from baseline; sustained 80% reduction in the number of cigarettes/day and sustained smoking abstinence at week 24	Study start date: January 2013 Estimated study completion date: November 2013 Last verification: June 2014
Smoking Cessation in Women with Gynecological Conditions	NCT01989923 (ClinicalTrials.gov) Laura A Beebe, PhD (University of Oklahoma)	RCT	To compare two smoking cessation methods: traditional NRT and ENDS in patients with gynecological conditions (i.e., cervical dysplasia, cervical cancer, and lower genital tract dysplasia and cancer)	United States	Estimated enrollment: 30	1. NRT: 24-hour nicotine patches (either 21 mg or 14 mg patches) 2. Electronic cigarette: One "blu cig"; number of cartridges determined by asking each patient the number of packs currently smoked per day and multiplying 1.5 times the number of packs smoked per day	Reduction of number of cigarettes smoked per day; point prevalence abstinence at 7 and 30 days; smoking abstinence rates	Study start date: June 2013 Estimated study completion date: March 2014 Last verification: November 2013

Appendix G Table 2. Ongoing or Recently Completed Studies: Electronic Nicotine Delivery Systems (ENDS)

Study, Year initiated	Identifier Principal Investigator	Design	Aim	Location	Number of participants	Intervention description	Relevant outcomes	Current status
Electronic Cigarettes or Nicotine Inhaler for Smoking Cessation	NCT02004171 (ClinicalTrials.gov) Barney Vaughan, MD (New York State Psychiatric Institute/ Columbia University)	RCT	To evaluate the effectiveness of electronic cigarettes in smokers who are trying to quit smoking compared with a standard therapy, the nicotine inhaler	United States	Estimated enrollment: 40	1. Experimental: Electronic cigarette; 24 mg cartridge; 1-2 cartridges daily 2. Active comparator: Nicotine inhaler; 10 mg cartridge; max 16 cartridges daily	Number of cigarettes smoked over 24 hours; adverse effects	Study start date: December 2013 Estimated study completion date: June 2014 Last verification: December 2013
A Randomized, Parallel Group, Multi-Center Study to Evaluate the Safety Profile of the ITG e-Vapor Product (EVP) G1 Product	NCT02029196 (ClinicalTrials.gov) Jim Bush, MD (Covance Clinical Research Unit, UK)	RCT	To evaluate the safety and tolerability of an e-vapor product	United Kingdom	Estimated enrollment: 420	1. Experimental: e-vapor product (EVP) 2. Active comparator: Conventional cigarette	Clinical measures (i.e., vital signs, electrocardiogram, lung function testing, and other clinical laboratory parameters)	Study start date: December 2013 Estimated study completion date: June 2014 Last verification: January 2014
Spain-UK-Czech E-cigarette Study (SUKCES)	NCT01842828 (ClinicalTrials.gov) Peter Hajek, PhD (Queen Mary University of London)	RCT	To test the effect of adding electronic cigarettes to standard care on long-term validated outcomes	London, Madrid, Prague	Estimated enrollment: 350	1. Standard care 2. Active comparator: Standard care plus electronic cigarettes	Carbon monoxide-validated abstinence rates at 24 weeks post-TQD	Study start date: December 2013 Estimated study completion date: June 2015 Last verification: March 2014

Appendix G Table 2. Ongoing or Recently Completed Studies: Electronic Nicotine Delivery Systems (ENDS)

Study, Year initiated	Identifier Principal Investigator	Design	Aim	Location	Number of participants	Intervention description	Relevant outcomes	Current status
Antismoking Effects of Electronic Cigarettes in Subjects with Schizophrenia and Their Potential Influence on Cognitive Functioning (SCARIS)	NCT01979796 (ClinicalTrials.gov) Eugenio Aguglia Pasquale Caponnetto Giuseppe Minutolo Riccardo Polosa (University degli Studi di Catania)	RCT	To evaluate the effects of electronic cigarettes in smokers with schizophrenia	Italy	Estimated enrollment: 153	1. Experimental: Electronic cigarette 24 mg nicotine 2. Sham comparator: Electronic cigarette 0 mg nicotine 3. Placebo comparator: Nicotine free inhalator	Smoking abstinence rates	Study start date: September 2014 Estimated study completion date: September 2015 Last verification: November 2013
Smoking Cessation and Reduction in Depression (SCARID)	NCT02124187 (ClinicalTrials.gov) Eugenio Aguglia Pasquale Caponnetto Giuseppe Minutolo Maria Salvina Signorelli Riccardo Polosa (University degli Studi di Catania)	RCT	To investigate the efficacy and safety of electronic cigarettes in depressed smokers not intending to quit	Italy	Estimated enrollment: 129	1. Experimental: Electronic cigarette 24 mg nicotine for 12 weeks 2. Sham comparator: Electronic cigarette 0 mg nicotine for 12 weeks 3. Placebo comparator: Nicotine free inhalator for 12 weeks	Smoking abstinence rates	Study start date: February 2015 Estimated study completion date: February 2016 Last verification: April 2014
A Multi-Center Study to Evaluate the Safety of Use of Electronic Vapor Products (EVP) for Two Years	NCT02143310 (ClinicalTrials.gov) Jim Bush, MD (Covance Clinical Research Unit, UK)	Interventional study with single group assignment	To evaluate the safety and tolerability of an e-vapor product over two years	United Kingdom	Estimated enrollment: 420	1. Experimental: e-vapor product (EVP)	Changes from baseline clinical measures (i.e., vital signs, electrocardiogram, lung function testing, and other clinical laboratory parameters)	Study start date: May 2014 Estimated study completion date: May 2016 Last verification: May 2014

Appendix G Table 2. Ongoing or Recently Completed Studies: Electronic Nicotine Delivery Systems (ENDS)

Study, Year initiated	Identifier Principal Investigator	Design	Aim	Location	Number of participants	Intervention description	Relevant outcomes	Current status
The Efficacy and Safety of Electronic Cigarettes: a 5-year Follow-up Study	NCT01785537 (ClinicalTrials.gov) Lamberto Manzoli, MD, MPH (University of Chieti)	Prospective cohort	To evaluate the long-term efficacy and safety (in terms of smoking-related serious diseases requiring hospitalization) of e-cigarette smoking, comparing its health effect s with those of traditional cigarette smoking and mixed electronic and traditional cigarette smoking	Italy	Estimated enrollment: 1050	1. Traditional cigarette smokers only 2. Electronic cigarette users only 3. Mixed	Smoking abstinence rates; change from baseline in the number of traditional cigarettes smoked; change in the average self-reported number of traditional cigarettes smoked per day	Study start date: October 2013 Estimated study completion date: December 2018 Last verification: November 2013
Can using nicotine as a long-term substitute enhance smoking cessation over using it only as a cessation aid?	ACTRN 12612001210864 (Australian New Zealand Clinical Trials Registry) Coral Gartner (The University of Queensland)	RCT	To examine the effectiveness of short-term use of NRT vs. short- or long-term use of NRT vs. short- or long-term use of NRT or ENDS for smoking cessation in cigarette smokers	Australia	Estimated enrollment: 1600	Combination of varying levels of self-help materials, NRT, advice, or electronic nicotine delivery systems	Continuous abstinence measures; 7-day point prevalence abstinence measures	Not yet recruiting

Appendix G Table 3. Ongoing Systematic Reviews

Study, Year initiated	Study designs included	Follow-up	Population	Intervention	Comparator	Relevant outcomes	Current status
Eisenberg, 2013 PROSPERO CRD42014007105	RCTs	12 months	Adult smokers	At least one first-line smoking cessation therapy (varenicline, bupropion, NRT, or behavioral therapy).	Placebo or at least one other first-line smoking cessation therapy	Smoking cessation; adverse events	Ongoing Estimated completion date: October 2015
Kelly, 2013 PROSPERO CRD42013004803	RCTs, SERs	≥ 6 months	Smokers of any age or sex either in the general populations or in more specific populations [co morbidities; mental illness; CVD; COPD; diabetes; pregnant women; and heavy smokers]	buproprion, varenicline, nicotine replacement therapies combined with behavioral support programs.	Placebo, no therapy or standard care, monotherapy or head-to-head of included interventions stated.	Smoking cessation; adverse events	Ongoing Estimated completion date: September 2013
Khanna, 2012 Cochrane protocol	RCTs	NR	Adult smokers with schizophrenia or related disorders	Physician advice	Usual care	Smoking cessation, quality of life, adverse events	Protocol published 2012 Estimated completion date: NR
Moffatt, 2014 PROSPERO CRD42014010128	RCTs or secondary analyses from RCTs of smoking cessation interventions	NR	Adult smokers aged ≥65, or a broader age-range of participants if sub-analyses were provided for smokers aged ≥65	Any patient-level smoking cessation strategies alone or in combination with other strategies	Usual care or placebo	Smoking cessation	Ongoing Estimated completion date: September 2014
Thomas, 2013 PROSPERO CRD42014009224	RCTs	NR	Adults prescribed varenicline	Varenicline (1 mg twice a day)	Placebo	Neuropsychiatric adverse events (suicide [fatal self-harm], nonfatal self- harm [parasuicide and attempted suicide], suicidal ideation and depression)	Ongoing Estimated completion date: August 2014