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Interventions for Tobacco Cessation in Adults, Including Pregnant Women: An Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We undertook this systematic review to support the U.S. Preventive Services Task Force in updating its 2015 recommendation on tobacco cessation interventions for adults, including pregnant women. Our review addressed the effectiveness and safety of pharmacotherapy, behavioral interventions, and electronic cigarettes for tobacco cessation.

Data Sources: We conducted an overview of reviews for evidence related to pharmacotherapy and behavioral interventions among the general adult population and for behavioral interventions among pregnant women. We searched the following databases and organizations' websites to identify existing reviews through April 2019: 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, the Canadian Agency for Drugs and Technologies in Health, Center for Disease Control and Prevention's Guide to Community Preventive Services, the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (formerly the Institute of Medicine), the National Health Service Health Technology Assessment Programme, and the Surgeon General. We conducted a search for primary evidence related to the effectiveness and safety of electronic cigarettes (through May 2020) and pharmacotherapy among pregnant women (through May 2020) and did not rely on existing systematic reviews for this evidence. We conducted ongoing surveillance for relevant literature through September 25, 2020.

Study Selection: For the overview of reviews, we included reviews with or without meta-analysis 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. For primary evidence related to the effectiveness and safety of electronic cigarettes among adults and pharmacotherapy among pregnant women, we included randomized controlled trials and large observational studies that reported health or cessation outcomes at 6 months or more followup or adverse events at any time point. For all evidence, we conducted critical appraisal of all provisionally included reviews and excluded reviews rated as having "critically low" credibility according to AMSTAR-2 criteria and individual studies rated as "poor" quality according to study design-specific risk-of-bias criteria. Data were abstracted by one reviewer and confirmed by another.

Data Analysis: We grouped reviews based on population and intervention and 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 but presented pooled analyses and existing point estimates from included reviews. We narratively synthesized the primary evidence for electronic cigarettes among adults and pregnant women and medications for smoking cessation among pregnant women and where appropriate, conducted random-effects meta-analyses to pool study results.

Results: We included 67 systematic reviews, 33 of which served as the basis for the primary findings. While this review was broadly scoped to include abstinence of all tobacco products, the

primary outcome in all cases was abstinence from combustible cigarette smoking. Among adults, combined pharmacotherapy and behavioral interventions significantly increased smoking abstinence by 83 percent versus usual care or minimal support control groups not using medication (risk ratio [RR] 1.83 [95% confidence interval [CI], 1.68 to 1.98]). Furthermore, all seven FDA-approved medications for smoking cessation were found to be effective in increasing smoking quit rates compared with placebo or nondrug arms at 6 or more months followup. The pooled RR for abstinence for nicotine replacement therapy (NRT, all forms) was 1.55 (95% CI, 1.49 to 1.61), for bupropion, 1.64 (95% CI, 1.52 to 1.77), and for varenicline, 2.24 (95% CI, 2.06 to 2.43). Combined NRT versus a single form of NRT showed a statistically significantly greater cessation effect (RR 1.25 [95% CI, 1.15 to 1.36]). Pooled analysis of trials directly comparing NRT and bupropion did not suggest a difference between the two types of pharmacotherapy; however, varenicline has been shown to be superior to both NRT and bupropion in achieving abstinence at 6 months or greater, although there are fewer trials testing these differences. Although less evidence is available, certain medications such as nortriptyline and cytisine used for tobacco cessation have shown potential benefits. None of the drugs were associated with serious adverse events, including major cardiovascular adverse events or serious neuropsychiatric events.

Compared with various controls, behavioral interventions such as in-person advice and support from clinicians including physician advice, nurse advice, individual counseling with a cessation specialist, group behavioral interventions, telephone counseling, mobile phone-based interventions, interactive and tailored internet-based interventions, and the use of incentives had modest but significantly increased relative smoking cessation at 6 or more months (15% to 88% range in relative effects). 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. There was a lack of clear benefit of motivational interviewing, decision aids, print-based, nontailored self-help materials, real-time video counseling, biofeedback (feedback on smoking exposure, smoking-related disease, or smoking-related harms), exercise, acupuncture, hypnotherapy, and system change interventions compared with controls; however, there was substantially less evidence related to each of these interventions. While some reviews found evidence of potential effect modification by specific intervention, population, or study design characteristics, there was no one factor that consistently predicted greater treatment effects, and nearly every subgroup analysis was found to be statistically significant. Few reviews on behavioral interventions captured information on potential harms, and none suggested serious adverse events that arose.

We identified five trials that addressed the effectiveness and harms of the use of electronic cigarettes among adults. No trials testing the effects of electronic cigarettes for smoking cessation among pregnant women were identified. Results were mixed on smoking cessation effectiveness at 6 to 12 months among smokers intending to quit when compared with placebo devices or NRT. Four additional trials also reported on potential short-term harms of electronic cigarette use for cessation; none suggested relatively higher rates of serious adverse events.

Among pregnant women, smoking cessation during late pregnancy was greater among women receiving any type of behavioral intervention, with evidence most clear for counseling versus controls (RR 1.31 [95% CI, 1.16 to 1.47]). Behavioral interventions were also associated with an increase in mean birthweight of babies as well as a decreased risk of low birth weight. We

identified one new trial of NRT among pregnant women, but no new trials testing the effects of bupropion or varenicline in this population. For NRT, rates of validated cessation among women allocated to NRT (5.4% to 28.2%) compared with placebo (5.0% to 25.4%) were not statistically different (pooled RR 1.11 [95% CI, 0.79 to 1.56]). Benefits of NRT on infant health outcomes were seen in a few trials, but that evidence was limited. There was no clear evidence of harms from behavioral interventions or associated with NRT use during pregnancy, but harms also could not be ruled out given sparse reporting, low statistical power for evaluating rare harms, and limitations of observational study comparisons.

Limitations: The comprehensiveness of our overview of reviews is limited by the recency and quality of the source reviews; with exceptions, we did not describe or cite individual trials because of the large volume of trials represented in the reviews. Furthermore, there are a limited number of trials testing the benefits and harms of electronic cigarettes among adults as well as the use of medications to assist pregnant women stop smoking. Such sparsity in research hampers our ability to make any robust conclusions about their effectiveness and potential harms.

Conclusions: There is strong evidence that a range or pharmacological and behavioral interventions, both individually and in combination, are effective in increasing smoking cessation in adults. Moreover, behavioral interventions can help pregnant women stop smoking. Data on the effectiveness and safety of electronic cigarettes for smoking cessation among adults are limited as are data on the use of tobacco cessation pharmacotherapies among pregnant women. Future research should focus on direct comparisons between different combinations and classes of drugs, adaptations of interventions for diverse populations, and the efficacy and safety of electronic cigarettes.

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Chapter 1. Introduction

Purpose

The Agency for Healthcare Research and Quality (AHRQ) has requested an updated evidence report on tobacco cessation interventions for adults and pregnant women. This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2015 recommendation on behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women.[1]

Condition Definition

Tobacco is a plant grown for its leaves, which are dried before being put in tobacco products. Tobacco contains nicotine, an ingredient that causes addiction, as well as many other harmful chemicals within the tobacco itself or created by burning it. Tobacco can be consumed in many combustible configurations including cigarettes, pipes, cigars, cigarillos, little cigars, bidis (tobacco wrapped in tendu or temburni leaves), kreteks (clove cigarettes), roll-your-own tobacco products, and through a hookah or waterpipe and noncombustible formats including chew, snuff including snus, nicotine pouches, nicotine gels, and dissolvable tobacco as strips, sticks, or lozenges.. Effective August 2016, the United States Food and Drug Administration (FDA) extended its regulatory authority to all other products made from or containing nicotine derived from tobacco, including electronic nicotine delivery systems (ENDS) (e.g., electronic cigarettes [e-cigarettes], e-hookah, e-cigars, vape pens, advanced refillable personal vaporizers, and electronic pipes) as well as components or parts intended or reasonably expected to be used with tobacco products or tobacco-derived nicotine. E-cigarettes intended for medical therapeutic purposes are subject to FDA regulations related to pharmaceuticals and medical devices rather than FDA regulations related to tobacco products. Companies that wish to make such claims must apply to the FDA's Center for Drug Evaluation and Research.[2, 3] Currently, no e-cigarettes are approved for therapeutic use as smoking cessation devices. In this review, given the regulatory environment in the U.S. regarding e-cigarettes, the use of e-cigarettes is included as both a tobacco product (for which we sought evidence related to quitting e-cigarette use) and as a potential smoking cessation aid (for which we sought evidence related to using e-cigarettes to quit combustible smoking).

Electronic nicotine delivery systems are a diverse group of products that produce a heated aerosol that users inhale from a mouthpiece. Electronic cigarettes (i.e., e-cigarettes or e-cigs) range in design but share certain components: a battery, heating coil, atomizer (transforms e-liquid to an aerosol), cartridge containing the e-liquid, and a mouthpiece. Users draw on the mouthpiece, activate the heating element, and inhale the aerosol. The liquid solution (i.e., e-liquid, juice) contains propylene glycol and/or glycerol (glycerin), with various levels of nicotine (including no nicotine).[4] Other components of the solution can include water and various additives including flavorings that vary among brands in presence and amount.[4] Early generation devices closely resembled cigarettes and were disposable or partly disposable; second-generation devices (i.e., vape pens) are rechargeable (most have a USB charger) and have customizable

looks and tip.[5] Later designs reflect a diverse set of products that may be square or rectangular and bear little resemblance to cigarettes. Many can be customized by the user and are referred to as modified vape devices (mods).[5] Box-style mods allow greater customization (e.g., wattage, temperature control) and are generally larger and more powerful than the previous two e-cigarette types. The more recent generation of e-cigarettes, including JUUL, Suorin and NJOY Ace, retail brands of e-cigarettes shaped like USB drives, are smaller and simpler than mods and are not refillable but use a pod that clicks onto the device to deliver the e-fluid (often referred to as pod mods). These devices typically have higher nicotine concentrations and utilize nicotine salts, which allows for higher levels of nicotine to be more palatably inhaled than free-base nicotine and can increase the rate of nicotine delivery as compared with earlier generations of e-cigarettes.[6, 7] Sales of JUULs increased markedly from 2015 to 2017, and JUUL is now the largest retail brand of e-cigarettes in the United States, accounting for more than half of the market share in tracked retail channels.[8, 9] Because e-cigarettes are developed by a variety of manufacturers, the contents vary widely and in some cases are not consistent with product labeling.[4, 10-12]

Tobacco dependence refers to a psychologic state typified by tolerance and withdrawal where the body is dependent on nicotine for normal function. According to the Diagnostic and Statistical Manual of Mental Disorders (fifth edition, DSM-5), a tobacco use disorder is diagnosed when an individual uses tobacco for more than a year and a minimum of two features that relate to nicotine tolerance, withdrawal symptoms, and social and behavioral factors related to use (e.g., failure to attend to responsibilities and obligations due to tobacco use, continue use despite adverse social or interpersonal consequences).[13] In light of the significant harm that can result from even low-level exposure to cigarette smoke, both chronic tobacco use and dependence warrant clinical intervention.[14]

Prevalence and Burden

Tobacco smoking is the leading preventable cause of disease, disability, and death in the United States. According to a 2014 Surgeon General's Report, cigarette smoking and exposure to tobacco smoke resulted in more than 480,000 premature deaths annually in the United States.[15] Combustible cigarette smoking causes various forms of cancer, cardiovascular disease, respiratory disease, reproductive disorders, and other adverse consequences. 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.[15] In addition to causing multiple diseases, cigarette smoking can cause inflammation and impair immune function.[15] 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.[15-18]

There has been progress over the past several decades in reducing the use of tobacco products by U.S. adults. In 2019, an estimated 20.8 percent (50.6 million) of adults in the United States currently used any tobacco product.[19] Combustible tobacco products were used by 80.5 of current tobacco product users and 18.6 percent of the same population reported use of two or

more tobacco products. The most commonly used tobacco product was combustible cigarettes (34.1 million; 14.0%).[19] Estimates regarding current use of other tobacco products among adults in 2019 were: e-cigarettes, 4.5 percent (10.9 million); cigars, 3.6 percent (8.7 million); smokeless tobacco, 2.4 percent (5.9 million); and pipes, 1.0 percent (2.4 million).[19]

According to findings from the nationally representative Behavioral Risk Factor Surveillance System, the overall current e-cigarette use prevalence rose from 4.5 percent (approximately 11.2 million adults) to 5.4 percent (approximately 13.7 million adults) in 2016 and 2018 respectively.[20] The largest increase in prevalence occurred within the younger age group (18-24 years of age), which rose from 9.2 percent to 15.0 percent in 2016 to 2018 respectively. According to the same survey data, in 2018, e-cigarette use was highest among males (6.9%), young adults ages 18 to 24 (15.0%), respondents identifying their race as "other" (6.4%) and white (5.8%), those identifying as bisexual (12.5%) or lesbian/gay (10.7%), respondents with high school and some college education (6.6%), respondents below the poverty line (6.9%) and respondents reporting current combustible cigarette us (14.7%).[20]

Despite a reduction in tobacco product use in U.S. adults, during 2017-2018, the prevalence of current us of any tobacco product increased by 38 percent among high school students (from 19.6% to 27.1%) and by 29 percent among middle school students (from 5.6% to 7.2%).[21] The increase in tobacco use seen in this time period was driven by the considerable rise in e-cigarette use. Data from the 2011–2018 National Youth Tobacco Survey (NYTS), found that among high school students, current e-cigarette use increased from 1.5 percent in 2011 to 20.8 percent in 2018; with a 78 percent increase just between 2017 (11.7%) to 2018 (20.8%).[21] Similarly, for young adults ages 18 to 24 years, a significant increase in self-reported e-cigarette use was seen between 2017 (5.2%) and 2018 (7.6%) (difference, 2.4% [95% CI, 0.4% to 4.4%]) whereas there was no change among adults aged 25 to 44 years and a nonsignificant decrease in those aged 45 to 64 and 65 and older.[22]

Among adults, persistent disparities in tobacco use exist by age, sex, race/ethnicity, sexual orientation, education, income level, insurance and disability status, psychological status, and region.[19] In 2019, prevalence of current tobacco product use was higher among those ages 25 to 44 years (25.3%), 45 to 64 years (23.0%), and 18 to 24 years (18.2%) than among those age ≥65 years (11.4%), and higher among males (26.2%) than females (15.7%). By race and ethnicity, current tobacco use prevalence was highest among American Indian/Alaska Natives (29.3%), followed by non-Hispanic adults of other races (28.1%), whites (23.3%), and blacks (20.7%), Hispanic or Latino adults (13.2%), and Asians (11.0%). Prevalence of tobacco use was also higher among adults who were lesbian, gay, or bisexual (29.9%) than among heterosexual adults (20.5%). Prevalence also varied by education and income levels: It was higher among adults who had a GED (43.7%) than among those who had completed any other levels of education (ranging from 26.4% in those with 0-12 year of education (with or without a high school diploma) to 8.7% in those with a graduate degree), and higher among those who had an annual household income of <$35,000 (27.0%) than among those with higher incomes (ranging from 15.1% in those with annual household incomes ≥$100,000 to 22.0% in those with annual household incomes between $35,000 and $74,000). In 2019, there was higher prevalence of tobacco product use among those who were uninsured (30.2%), those insured by Medicaid (30.0%), or had other public insurance (25.6%) than among people covered by private health insurance (18.0%) or

Medicare only (11.4%). Prevalence was also higher among those who had a disability/limitation (26.9%) than among those who did not (20.1%), as well as among those who had Generalized Anxiety Scores (GAD-7) indicating mild (30.4%), moderate (34.2%), or severe (45.3%) anxiety than among those indicating no or minimal anxiety (18.4%). Additionally, by U.S. region, the Midwest (23.7%) and South (22.9%) had higher prevalence of tobacco product use than the West (16.4%) or Northeast (18.5%).[19]

Among pregnant U.S. women who gave birth in 2016, 7.2 percent reported smoking cigarettes while pregnant.[23] The prevalence of smoking during pregnancy was highest among women ages 20 to 24 years (10.7%), followed by women ages 15 to 19 (8.5%) and 25 to 29 years (8.2%). Additionally, prevalence of smoking during pregnancy was highest for women with a high school diploma or GED (12.2%), followed by women with less than a high school diploma (11.7%) and women with some college or an Associate degree (7.9%) while prevalence was lowest among women with a master's degree of higher (0.4%). Similar to trends in the general adult population, Non-Hispanic American Indian or Alaska Native women had the highest prevalence of smoking during pregnancy (16.7%), followed by white women (10.5%), black (6.0%), Native Hawaiian or other Pacific Islander (4.5%), Hispanic women (1.8%) and Asian women (0.6%).[23] Additionally, from 2014 to 2017, 3.6 percent of pregnant women ages 18 to 44 years reported current use of e-cigarettes, a proportion that was not statistically significantly different among non-pregnant women in the same age group (3.3%).[24]

According to 2016-2018 Behavioral Risk Factor Surveillance System Survey data, approximately 2.2 percent of adult pregnant women (ages 18 to 49) reported current e-cigarette use.[25] The prevalence of current e-cigarette use among pregnant women was highest among the younger age group, aged 18 to 24 years (3.2%), followed by pregnant women ages 25 to 29 years (2.3%). In addition, the prevalence of current e-cigarette use among pregnant women was highest in those reporting white race (63.3%), single marital status (57.6%), high school and some college education (66.6%), and employed (61.7%). The prevalence of current e-cigarette use among this population almost doubled from 2016 to 2018 (1.9% and 3.8% respectively).[25]

Etiology and Natural History

Initiation of cigarette smoking typically begins in early adolescence at an average age of 15 years.[17] 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 cigarette smoking become daily smokers.[17] Among adolescents, symptoms of dependence have been reported at even low levels of cigarette consumption (e.g., two cigarettes once a week).[26, 27]

Tobacco dependence is a chronic condition and the majority of users make multiple quit attempts before achieving lasting success.[28] According to the NHIS, approximately two-thirds of all people who smoked cigarettes in 2015 (68%) reported they were interested in quitting smoking, and 55.4 percent of these smokers had made a quit attempt during the previous year, although less than one-third had used evidence-based cessation treatments and less than one in 10 were

successful in quitting in the previous year.[29] One study estimated that 22 percent of smokers relapsed within 3 months;[30] however, long-term follow-up is recommended because successful quitters remain at risk of relapse for several years after smoking cessation.

Research shows that the appearance of withdrawal symptoms early in the quit-attempt period is negatively associated with the ability to remain abstinent and avoid relapse.[17] On average, a second lapse (i.e., one instance of smoking, even a puff) occurs with 24 hours of the first lapse, and lapse to relapse (i.e., return to one's baseline level of smoking) occurs 3 to 5 weeks after the cessation attempt.[17] Factors associated with relapse include higher severity of nicotine dependence, daily smoking onset at younger age, higher number of prior quit attempts, being female, presence of psychiatric symptoms (mainly anxiety and depression symptoms), and higher body mass index.[17] The rate of relapse is inversely related to the duration of continuous abstinence (i.e., the risk of relapse decreases with longer abstinence). For example, one study found the relapse rate among those who achieved up to 11 months of abstinence was consistently above 50 percent, dropping to 36 percent after 2 years of abstinence and 25 percent after 5 years of abstinence, then stabilizing at around 10 percent after 30 years of abstinence.[31]

Tobacco Cessation Interventions

Various pharmacological and behavioral methods are available to assist adults quit tobacco use. Behavioral interventions and pharmacotherapy are believed to have complementary modes of action and independently increase the chances of maintaining long-term abstinence.[14]

Pharmacotherapy Tobacco Cessation Interventions

Seven FDA-approved over-the-counter (OTC) and prescription medications for treating tobacco dependence are available.[32] These include three OTC nicotine replacement therapy (NRT) products (transdermal nicotine patches, nicotine lozenges, and nicotine gum), two prescription-only nicotine replacement therapy products (nicotine inhaler and nasal spray [Nicotrol®]), and prescription-only bupropion hydrochloride sustained release (Zyban® and generic form; referred to as bupropion hereafter) and varenicline tartrate (Chantix®), neither of which contains nicotine. Although Wellbutrin SR® is not indicated for smoking cessation treatment, it contains the same active ingredient as Zyban®. Other medications are used clinically to treat tobacco dependence, including clonidine (antihypertensive) and nortriptyline (antidepressant), but these are not FDA-approved for smoking cessation.[32, 33] Cytisine, a partial agonist of nicotine acetylcholine receptors, is available both with and without a prescription in eastern and central Europe[34] and is widely available internationally (including in the United States) through online vendors although not FDA-approved.[35]

Behavioral Tobacco Cessation Interventions

Specific behavioral interventions include 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 setting, mobile phone and text-messaging interventions, biomedical risk assessment, and combinations of these approaches. Behavioral interventions generally aim to 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 Cigarettes

There is a debate in the tobacco control community about the public health impact of e-cigarettes, how best to regulate them, and their role in tobacco cessation.[5, 36] Because e-cigarettes may offer both nicotine replacement and behavioral and sensory aspects similar to conventional cigarettes without the inhalation of tobacco smoke, they have the potential to serve as a tobacco cessation or harm reduction tool when used by smokers who transition completely to e-cigarettes.[37-39] Conversely, when taken up by nonsmokers (generally adolescents and young adults), e-cigarettes may serve as a pathway to nicotine addiction and tobacco smoking.[15] In addition, questions remain regarding the effectiveness of e-cigarettes for tobacco cessation as well as their impact on individual and population health, including the potential for progression to conventional tobacco use among adult nontobacco users, long-term dual use among current smokers, relapse among former smokers, and exposure to harmful or potentially harmful constituents in specific products.[14, 15, 40-43]

Current Clinical Practice in the United States

In 2015, 68.0 percent of adult smokers wanted to stop smoking, 55.4 percent made a past-year quit attempt, 7.4 percent recently quit smoking, 57.2 percent had been advised by a health professional to quit, and 31.2 percent used cessation counseling and/or medication when trying to quit.[29] Among smokers who made quit attempts, 6.8 percent reported using counseling, 29.0 percent reported using medication, and 4.7 percent reported using both. Among those who used counseling, 4.1 percent used a telephone quitline, 2.8 percent used one-on-one counseling, and 2.4 percent used a stop-smoking clinic, class, or support group. Among smokers who used a medication to quit, 16.6 percent reported using a nicotine patch, 12.5 percent used nicotine gum or lozenges, 7.9 percent used varenicline, 2.7 percent used bupropion, and 2.4 percent used a nicotine spray or inhaler.[29]

The rates of counseling and treatment vary modestly depending on patients' age, race/ethnicity, gender, insurance status, health status, physician status, and physician specialty.[44, 45] Smokers aged 45–64 years (65.7%) and ≥65 years (65.7%) reported a higher prevalence of receiving advice to quit than did smokers aged 18–24 years (44.4%) and 25–44 years (49.8%).[45] Lower prevalence of receiving advice to quit were reported by Asian (34.2%), American Indian/Alaska Native (38.1%), and Hispanic (42.2%) smokers than by white smokers (60.2%); and by uninsured smokers (44.1%) than by smokers with any type of insurance (range = 56.8%–69.2%). Smokers reporting a disability/limitation or serious psychological distress reported a higher prevalence of receiving advice to quit than did smokers without these conditions (71.8% and 70.2%, respectively, vs 53.6% and 55.7%).[29, 45, 46] One survey found that 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%, respectively) than family or

obstetrics/gynecology physicians (23.5% and 19.7%). Psychiatrists ordered tobacco cessation prescriptions more than any other specialty (17.7%).[45]

A few physician surveys and qualitative studies suggests that physician screening for e-cigarette use is limited, but report that some physicians recommend the use of e-cigarettes as cessation devices. When surveyed in 2013, two-thirds of a sample of 787 North Carolina physicians indicated that e-cigarettes were a helpful aid for smoking cessation, 13 percent incorrectly believed that e-cigarettes were approved by the FDA for smoking cessation, and 35 percent recommended them to their patients.[47] Conversely, a survey of Kansas family physicians published in 2017 found that 82 percent would not recommend e-cigarettes for smoking cessation.[48] A national survey of primary care physicians, pulmonologists, surgeons, and anesthesiologists conducted in 2015 found that approximately 54.5 percent agreed with a statement that e-cigarettes could help patients quit smoking, and 37.9 percent have at some point recommended electronic cigarettes to their patients that smoke.[49]

Screening for e-cigarette use varies by practice and risk demographics. 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.[50, 51] One study of patient-reported screening prevalence from the 2013–2014 National Survey on Drug Use and Health showed that patients with anxiety, depression, and substance abuse disorders were more likely to be screened for noncigarette tobacco product use (88.6%, 79.6%, and 79.4%, respectively) than respondents with no reported mental health conditions (77.8%).[52]

Recommendations of Others

The 2015 USPSTF recommendation and 2008 Public Health Service (PHS) Guideline[53] (the basis of the 2008 USPSTF recommendation) are endorsed by or are generally consistent with the recommendations of other national and international organizations, including those from the American College of Physicians and American Medical Association,[54, 55] American Family Physicians,[56] and the American Dental Association.[57] The 2020 Surgeon General's report on Smoking Cessation similarly concluded that smoking cessation medications approved by the FDA and behavioral counseling are cost-effective cessation strategies and increase the likelihood of successfully quitting smoking, particularly when used in combination.[14] 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.[58]

The World Health Organization released recommendations for the prevention of tobacco use during pregnancy in 2013[18] that were based on an overview of reviews and a panel of experts' ratings of the quality of the evidence. The panel made a strong recommendation for advice and psychosocial interventions for pregnant women who were smokers. It 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. ACOG recommendations for smoking cessation during pregnancy[59] are also consistent with the 2015 USPSTF recommendations[1] and the 2008 PHS Guideline.[53]

Several national and professional organizations have issued recent recommendations regarding screening for and use of e-cigarettes among adults.[14, 43, 59-64] Many recommend that e-cigarette use should be part of tobacco screening questions and that those who smoke or vape should be advised to quit *all* nicotine products and be provided with tobacco cessation interventions. Recommendations regarding the use of e-cigarettes as an aid for quitting use of other tobacco products (namely combustible cigarettes) are mixed: the 2020 Surgeon General's report on Smoking Cessation concluded that that there is presently **inadequate evidence** to conclude that e-cigarettes, in general, increase smoking cessation.[14] A recent 2019 American College of Preventive Medicine guideline states that clinicians should advise patients that e-cigarettes are not considered evidence-based smoking cessation therapy; but that a shared-decision making approach may be necessary if patients have failed or refused other therapies and are more willing to try e-cigarettes to cut down or quit smoking.[63] ACOG recommends against the use of e-cigarette products by pregnant and postpartum individuals, children and adolescents, and adults who currently do not use tobacco products.[61] The American Cancer Society (2019) does not recommend the use of e-cigarettes as a cessation method[62] and the American Heart Association concluded in its 2014 position paper that there was not enough evidence for clinicians to counsel their patients to use e-cigarettes as a primary cessation aid.[43] Key policy recommendations by organizations including the AMA,[65] Surgeon General,[66, 67] and the American Association for Cancer Research and the American Society of Clinical Oncology[65] have also been published in support of Federal, State, and local regulation of e-cigarettes, most specifically policies aimed at restricting the sale, distributions, marketing, and advertising of e-cigarettes to youth as well as smoke-free policies that include e-cigarettes.

Previous USPSTF Recommendation

In 2015, the USPSTF issued four recommendation statements (**Table 1**).[1] Two "A" grade recommendations were given for behavioral and pharmacotherapy interventions for adults and for behavioral interventions for pregnant women, whereas two "I" statements were issued for pharmacotherapy interventions for pregnant women and the use of e-cigarettes for tobacco cessation among adults and pregnant women. The 2015 recommendation updated and was consistent with the 2009 and 2003 recommendations.[68] In both years, the USPSTF recommended that clinicians ask all adults about tobacco use and provide interventions for smoking cessation for those who use tobacco products (A recommendation). It also recommended that clinicians ask all pregnant women about tobacco use and provide augmented, pregnancy-tailored counseling for those who smoke (A recommendation). 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".[28, 69]

Chapter 2. Methods

Scope and Purpose

This is an update of our 2015 review.[70, 71] Consistent with that review, we relied primarily on an overview of reviews method for this update. In general, an overview of reviews focuses on a broad condition or problem for which there are two or more potential interventions. The overview of reviews approach was the most appropriate approach for our update because of the large number of tobacco cessation trials and the availability of multiple systematic reviews on the subject. To conduct this overview of reviews, we: 1) searched for reviews; 2) selected reviews; 3) assessed the credibility of the reviews; 4) determined the use of reviews; 5) abstracted review details and findings; and 6) synthesized findings across reviews. A typical Analytic Framework, Key Questions (KQs), and inclusion/exclusion criteria are outlined as they relate to the objectives of the overview of reviews. We did not search for original research (with the exceptions noted below), replicate quality rating or data abstraction of original studies, or replicate review-specific meta-analyses.

Evidence for pregnant women was synthesized separately from evidence for the general adult population given the unique health risks of tobacco smoking for both women and children, physiological differences during pregnancy that can affect nicotine withdrawal symptoms, generally higher motivation to quit among pregnant than nonpregnant adults, and the potential different benefits and harms of various cessation treatments.

Given the 2015 USPSTF conclusions of insufficient evidence for 1) the benefits and harms of e-cigarettes for tobacco cessation and 2) the benefits and harms of pharmacologic tobacco cessation interventions among pregnant women, we decided *a priori* to conduct a de novo systematic review (i.e., an original search and synthesis of primary evidence) related to these specific areas. 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 (2014-present) reviews were identified for the topic.

Key Questions and Analytic Framework

With input from the USPSTF, we developed an Analytic Framework (**Figure 1**) and three KQs, using the USPSTF's methods to guide the literature search, data abstraction, and data synthesis.

1. Do tobacco cessation interventions improve mortality, morbidity, and other health outcomes in adults who currently use tobacco, including pregnant women?
2. Do tobacco cessation interventions increase tobacco abstinence in adults who currently use tobacco, including pregnant women?
3. What harms are associated with tobacco cessation interventions in adults, including pregnant women?

Data Sources and Searches

We searched the following databases for relevant systematic reviews through April 2019 (with active surveillance through September 2020): 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 A**). In addition to these database searches, we searched the websites of the following organizations: AHRQ, the Canadian Agency for Drugs and Technologies in Health, CDC's Guide to Community Preventive Services, Health and Medicine Division of the National Academies (formerly the Institute of Medicine), the NHS Health Technology Assessment Programme, and the U.S. Surgeon General. We restricted our searches to articles in the English language published since January 2014. We also examined the reference lists of all our included reviews to identify other reviews 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, and the Centre for Reviews and Dissemination PROSPERO register.

In addition to the search for reviews, we conducted two separate searches for primary evidence.

The first search focused on studies addressing the use of e-cigarettes for tobacco cessation. We conducted searches in the following databases: CDSR, Cochrane Central Register of Controlled Clinical Trials (CENTRAL), PsycInfo, PubMed, and Scopus, from January 2014 through May 2020 (**Appendix A**).

The second search centered on pharmacotherapy tobacco cessation interventions among pregnant women; we conducted searches in Medline, CENTRAL, PubMed, PsycInfo from January 2014 through May 2020 (**Appendix A**).

We conducted ongoing surveillance for relevant primary literature through January 23, 2020 and for Cochrane systematic reviews through September 25, 2020 and have updated the review with new evidence as it is published.

We also reviewed the reference lists of related systematic or narrative reviews to identify studies for potential inclusion and searched *ClinicalTrials.gov* for relevant ongoing trials 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 sources directly into EndNote® X9.

Study Selection

We developed criteria for inclusion and exclusion of systematic reviews based on our previous review (**Appendix A 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 and 2) were published in English from January 2014 to present. We included reviews focused on specific interventions (e.g., NRT, group counseling) and specific subpopulations (e.g., persons with serious mental illness). We considered reviews published by Cochrane as well as other non-Cochrane reviews. We excluded nonsystematic narrative reviews and other reviews of reviews. We excluded reviews that only or primarily evaluated interventions among children and adolescents and broader public health strategies. We included only the most recent version of updated reviews.

We outlined separate inclusion and exclusion criteria when considering primary evidence related to e-cigarettes and pharmacotherapy interventions among pregnant women. For primary evidence related to the benefits (KQ 1-KQ 2) and safety (KQ 3) of e-cigarettes, we included randomized controlled trials (RCTs) in which smokers were randomized to e-cigarettes or a control condition, such as a placebo/placebo device, a no-intervention condition, or another active tobacco cessation intervention (e.g., NRT, counseling). We included cohort studies with sample sizes of 1,000 participants or more. We included studies only if they reported a health outcome (KQ 1) or a measure of tobacco abstinence (KQ 2) at least 6 months after baseline assessment or adverse events (AEs) (KQ 3) at any point after treatment started. We excluded studies that only reported intermediate smoking outcomes (e.g., desire to smoke, withdrawal symptoms, quantity of cigarettes smoked). We required that studies take place in developed countries defined as "very high" on the 2015 Human Development Index (HDI) of the United Nations (http://hdr.undp.org/en/statistics).

For pharmacotherapy interventions among pregnant women, we used the criteria outlined in the review by Coleman and colleagues.[72] Accordingly, we included RCTs that permitted assessment of the independent effects of any type of 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. In addition, and unique from the Coleman review, we included large cohort studies (n>1000) that compared pregnant women who were exposed versus not exposed to medications for smoking cessation. We excluded quasi-randomized, crossover, and within-participant designs, and required that studies take place in countries deemed "very high" on the Human Development Index.

Two reviewers independently screened the abstracts and titles of all records identified in the searches, using the inclusion and exclusion criteria as a guide for identifying eligible studies. 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, although disagreements were minimal and easily resolved. All reviews were conducted in DistillerSR (Evidence Partners, Ottawa, Canada). We kept detailed records of all included and excluded studies (and reasons for exclusion) during full-text review.

Quality Assessment and Data Abstraction

We used the AMSTAR 2 (Assessment of Multiple Systematic Reviews) tool to rate the credibility of the systematic reviews under consideration for inclusion.[73] The AMSTAR 2 tool contains 16 items that relate to the planning and conduct of the review (**Appendix A Table 2**).

We rated our overall confidence in the results of each review according to published guidance: a rating of "high" reflects that the review had zero or one noncritical weakness; "moderate" indicates the review was judged to have more than one noncritical weakness; "low" means the review was judged to have one critical flaw with or without noncritical weaknesses or multiple noncritical weaknesses; and "critically low" signifies that more than one critical flaw was present. In line with USPSTF criteria for primary evidence, we excluded reviews rated as critically low because they would not provide an accurate and comprehensive summary of the available evidence. We included low credibility reviews but rarely relied on them for the main results. One reviewer completed the AMSTAR 2 tool for all provisionally included reviews, and for all reviews that were rated critically low a second reviewer provided an independent assessment with the same tool.

For individual studies, we used criteria developed by the USPSTF to assess the quality of included evidence (**Appendix A Table 2**).[74] 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 the appropriateness of the statistical procedures, including methods for handling missing data. At least two independent reviewers assessed the quality of the primary evidence, and we resolved discrepancies through consultation with a third reviewer and discussion. We applied the typical USPSTF quality scores (i.e., good quality, fair quality, or poor quality) after reviewing the number and seriousness of the threats to validity. Those rated as poor quality contained a serious flaw or flaws that we felt likely biased or invalidated the results and were excluded from this review.

We abstracted data from each included review and primary study into detailed abstraction forms using DistillerSR. For all included evidence, one reviewer completed primary data abstraction, and a second reviewer checked all data for accuracy and completeness.

Data Synthesis and Analysis

Given the large number of reviews that met our eligibility criteria and the overlapping scope and evidence between many of them, we developed a method to identify one or more reviews within each population and intervention subgroup that represented the most current and applicable evidence. These reviews serve as the basis for the main findings (called primary reviews hereafter). **Box 1** describes the full set of criteria we applied to identify the primary reviews for each population and intervention. First, we categorized all included reviews according to the type of tobacco cessation intervention (i.e., distinct types of pharmacotherapy, behavioral, and/or combination interventions) and population (e.g., adults, pregnant women). Within each group, we listed the reviews in chronological order by the last search date (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 comprehensiveness and noted concordance and discordance in the included primary literature. When we encountered highly discordant bodies of evidence, we sought an explanation for the difference by examining the inclusion and exclusion criteria. 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. We reviewed the remaining reviews for complementary or discordant findings. 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 Primary Systematic Reviews Compared With Other Reviews for the Same Population and Intervention Group

1. The search strategy is more up to date.
2. The included studies apply inclusion/exclusion criteria that offer the most relevant and credible evidence (i.e., based on included study designs, populations, comparators, setting, followup >6 months, and outcomes).
3. There are more (or an equal number of) included studies of the ideal study design
4. Appropriately conducted pooled results are presented, with or without meta regression or subgroup analysis.
5. The quality of the review is better.

We summarized the characteristics of the primary evidence reviews in evidence tables but did not reanalyze individual study data. Instead, we reported the pooled analyses and existing point estimates presented in the included reviews. 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 available meta-analytic results. We also presented subgroup results related to the intensity or type of intervention, when available. 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.

In anticipation of sparse reporting of health outcomes (KQ 1), we decided a priori to synthesize any data related to health outcomes qualitatively. The primary outcome for KQ 2 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 or 30 days before followup and thus includes a mix of recent and continuous quitters).[75] Biochemical verification of self-reported abstinence was not required in most reviews, but validated outcomes were used when reported. 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.[75]

To evaluate health outcomes in pregnant women and neonates, we analyzed outcomes for all RCTs regardless of the control condition. Due to high statistical heterogeneity, we do not provide pooled effect estimates. Instead, we present descriptive forest plots comparing the NRT and control conditions for key reported perinatal health outcomes (preterm birth, low birthweight, stillbirth, birthweight) and narratively describe the results of the individual studies. The calculated relative risks are presented for most outcomes, but for low birthweight, the odds ratios were calculated for some trials and combined with study reported odds ratios to allow for comparisons of this outcome across all studies reporting the outcome. For some studies, data necessary for comparing health outcomes were not available in the primary studies. In such instances, we used data reported in a recent Cochrane review that directly contacted study authors for relevant data.[72, 76]

For computing a pooled estimate across the included trials for pharmacotherapy smoking cessation among pregnant women, we used the DerSimonian and Laird model for pooling relative risks (RR) and used a restricted maximum likelihood model with the Knapp-Hartung correction for small samples to estimate the 95% CI interval.[77] We used Stata version 15.1 (StataCorp LP, College Station, TX) for all analyses. All significance testing was 2-sided, and results were considered statistically significant if the p-value was 0.05 or less.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ as follows. “High” indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. “Moderate” indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. “Low” indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of “insufficient” indicates that evidence is either unavailable or does not permit estimate of an effect.

For our overview of reviews method, we adopted the strength of the overall body of evidence assigned within the primary systematic review. In most cases, these grades were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group definitions, which consider study limitations, consistency of effect, imprecision, indirectness and publication bias. Where strength of evidence grades were not available, including for our own primary evidence syntheses, we adapted the EPC approach – which generally aligns with GRADE methodology – to assign an overall strength of evidence grade based on consensus discussions involving at least two reviewers.[78]

Expert Review and Public Comment

A draft Research Plan was posted on the USPSTF Web site for public comment from March 14 through April 11, 2018. In response to public comment, the USPSTF made the following changes to the research plan. First, reviews focused on relapse prevention interventions are

included. Second, the USPSTF clarified that the target condition includes use of any tobacco product, as regulated by the FDA, including cigarettes, roll-your-own tobacco, smokeless tobacco, cigars, pipe tobacco, dissolvables, smoking tobacco through a hookah or waterpipe, and e-cigarettes. Reviews limited to or including cessation of any of these tobacco products are included. Third, reviews limited to specific subpopulations of adults with high prevalence of tobacco use or at risk of tobacco use-related morbidity are included, as are results from credible subgroup analyses. Last, reviews of medications that are not approved as first-line tobacco cessation medications but are used off-label and are available in the United States are included. The USPSTF made other minor modifications and clarifications as appropriate, including clarifying that any intervention that takes place in primary care or that can feasibly be referred to from primary care are included. A final research plan was posted on the USPSTF Web site on July 26, 2018. We made no deviations from the final research plan in the conduct of this review.

A draft version of this report was reviewed by content experts, representatives of Federal partners, USPSTF members, and an AHRQ Medical Officer. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report. Additionally, a draft of the full report was posted on the USPSTF Web site from June 2, 2020 to June 29, 2020. A few comments were received during this public comment period. All comments were read and considered; minor editorial changes were made to the report based on these comments, but no changes were made to the evidence or to our conclusions.

USPSTF Involvement

We worked with four USPSTF members at key points throughout this review, particularly when determining the scope and methods and developing the Analytic Framework and KQs. The USPSTF members 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

This report addresses two populations of interest: the general adult population and pregnant women. Within each population, results are organized first by KQ and then by intervention-specific categories.

Evidence for Adults

Included Evidence

We identified 64 reviews that synthesized the benefits and/or harms of tobacco cessation interventions among adults, including those among an unselected population of adults and those limited to a specific subgroup of adults (**Table 2**).[79-142] Fifty-eight of these reviews were newly identified (published from 2014 to 2020) and six reviews were carried forward from our previous systematic review. The remaining reviews included in our previous report were excluded because more recent and comprehensive reviews on each population or intervention have been published. Of the 210 full-text articles that were reviewed, the most common reasons for exclusion were study design (i.e., not a systematic review; k=42), absence of prespecified outcomes or cessation outcomes at 6 months or more (k=27), and critically low-quality rating (k=23) (**Appendix B Figure 1**).

We designated 32 of the 64 reviews as primary reviews on smoking cessation interventions for general adult populations (**Table 2**). As described in the methods section, we chose these primary reviews based on their comprehensiveness, appropriateness (in scope and applicability), and critical appraisal ratings. **Table 3** lists the inclusion and exclusion criteria for each primary review. **Table 4** lists the characteristics of the included evidence for each primary review and **Table 5** presents the pooled results for tobacco cessation outcomes for all included interventions.

Eleven "ancillary" reviews had overlapping evidence with that synthesized in the primary reviews; results were consistent with the primary reviews in terms of statistical significance and effect magnitude and are not discussed further. An additional 21 reviews focused on specific subpopulations of adults (e.g., people with severe mental illness, smokeless tobacco users). Results of these subpopulation reviews were compared with results from general adult reviews; we only discussed findings of these subgroup reviews if they suggested substantive differences than that of the broader reviews. Seven of these reviews among specific subgroups presented results related to harms of medication use and are also included as main results. Characteristics of these additional reviews (ancillary and those limited to subpopulations) are provided in **Appendix C.**

Our review of the primary evidence on the use of e-cigarettes for tobacco cessation resulted in nine included trials (reported in 16 publications), five of which addressed tobacco cessation and all of which address potential harms (**Appendix B, Figure 2**).[143-158] Two of these trials were included in our previous review, and seven trials are new to this update.

Appendix D lists all included studies and **Appendix E** lists the excluded studies, with reasons for exclusion.

Credibility/Quality Assessment

We rated 29 of the reviews in adults as having high credibility, 26 as having moderate credibility, and the remaining 9 as having low credibility according to AMSTAR 2 criteria. Most of the main results (primary reviews) were based on reviews we rated as high or moderate credibility; only three reviews rated as low credibility were presented as main results given their unique foci (harms of varenicline, sex differences in the effectiveness of medications, and harms of varenicline use among smokeless tobacco users). Though they were rated as low credibility, the flaws noted in these reviews (e.g., lack of dual study selection, unclear ascertainment of funding of included studies, not accounting for risk-of-bias of studies in interpretation of the findings) are unlikely to invalidate the results we present from these reviews. We excluded 26 reviews as having very low credibility; these reviews had more than one critical flaw and thus, we felt could not be relied on to provide an accurate and comprehensive summary of the available evidence. Many of these critical flaws related to the search and selection of included studies (e.g., a partial search strategy, no dual selection of studies), a lack of a risk-of-bias assessment, very little information about the included studies, or an inappropriate data synthesis or analysis method. Of the 64 included reviews, 32 were Cochrane Collaboration reviews. These reviews are generally well-conducted, well-reported, and use similar robust methods for study selection and synthesis, strengthening our confidence in these findings.

We rated all eight trials of e-cigarettes as fair quality (**Table 6**). Major quality limitations of these trials included uncertain validity of randomization and allocation concealment procedures, differences in reasons for missing data across treatment groups, unclear blinding of outcome assessors, substantial crossover and relatively high loss to follow-up with unclear treatment of missing data.

Key Question 1. Do Tobacco Cessation Interventions Improve Mortality, Morbidity, and Other Health Outcomes in Adults Who Currently Use Tobacco?

Combined Pharmacotherapy and Behavioral Interventions

None of the included systematic reviews reported the effectiveness of combined pharmacotherapy and behavioral interventions on health outcomes, including mortality and tobacco-related morbidity.

Pharmacotherapy Interventions

None of the included systematic reviews that assessed pharmacotherapy interventions among a general adult population reported the effects of interventions on mortality, morbidity, or other

health outcomes.

Behavioral Interventions

One systematic review[125] reported the results from a single RCT[159] that evaluated the effect of a behavioral tobacco cessation intervention on health outcomes. In this trial, males considered to be at high risk of cardiorespiratory disease (n=1,445) were randomized to an intensive stop-smoking intervention that included advice, written materials, and one followup visit on health outcomes or a no intervention control group. At 20-year followup, in the intervention compared with the control group, total mortality was 7 percent lower, fatal coronary disease was 13 percent lower and lung cancer (death plus registrations) was 11 percent lower.[160] These differences were not statistically significant, reflecting low power and the diluting effects of incomplete compliance with the cessation advice in the intervention group, and a progressive reduction in smoking by men in the control group.[160]

E-Cigarettes

We did not identify any primary evidence on the use of e-cigarettes as tobacco cessation interventions that reported results related to health outcomes.

Key Question 2. Do Tobacco Cessation Interventions Increase Tobacco Abstinence in Adults Who Currently Use Tobacco?

Combined Pharmacotherapy and Behavioral Interventions

Primary Results

Only one review, the moderate-credibility review by Stead (2016), assessed the effect of combining pharmacotherapy and behavioral support for smoking cessation among adults.[127] The review included 53 trials (12 of which were new to this update) that enrolled 15 to 5887 participants. In a meta-analysis that combined 52 of the 53 trials, there was a statistically significant benefit of combined pharmacotherapy and behavioral interventions versus control on smoking cessation at 6 months' followup or longer (risk ratio [RR] 1.83 [95% confidence interval [CI], 1.68 to 1.98]; I^2=36%; k=52; n=19,488) (**Table 5**).[127] Average quit rates in these trials ranged from 2 to 50 percent (mean: 15.2%) among participants receiving pharmacotherapy and behavioral support versus 0 to 36 percent (mean: 8.6%) among participants randomized to a control group. The review found some evidence of asymmetry in a funnel plot, with an excess of smaller trials detecting larger effects, suggesting the possibility of publication or other bias; however, a sensitivity analysis removing the smaller trials did not have a marked effect on the pooled estimate.[127]

Control participants were offered usual care, self-help materials or brief advice on quitting that was of lower intensity than that given to intervention participants.[127] Studies limited to adolescents or pregnant women were excluded. About half of the studies were conducted in the

United States. A high proportion of trials were conducted in health care settings (e.g., primary care clinics, dental clinics, Veterans Administration medical centers) and/or recruited people with specific health needs (e.g., general and psychiatric hospital inpatients, patients awaiting admission for surgery, mental health patients, those with mild airway obstruction or COPD). In more than half of the trials (32/53, 60%), participants were required to be motivated to quit smoking for inclusion or were classified as likely to be interested in quitting; the remaining trials (21/53, 40%) did not select participants based on motivation to quit. The average age of participants typically ranged from low 40s to mid-50s.[127]

The included interventions typically offered or prescribed NRT; only seven trials offered bupropion or nortriptyline, and no trials offered varenicline.[127] There was a great deal of variation in the intensity (number of sessions) and format of behavioral support. The typical intervention involved multiple contacts with a trained specialist cessation adviser or counselor, including face-to-face contact with additional sessions often provided by phone. Most trials (28/53, 53%) offered between four and eight sessions and a quarter (13/53, 25%) offered more than eight sessions. Total planned intervention contact time typically ranged from 90 to 300 minutes. Specialized cessation counselors or trained trial staff delivered most of the interventions. A primary care provider was the main interventionist in only four included studies.[127]

Evidence of Effect Modification

The review by Stead conducted planned subgroup analyses by setting, participant motivation to quit, provider, intensity, and compliance with medication and behavioral support.[127] They found that the pooled effect of combined interventions was higher among 43 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 1.97 [95% CI, 1.79 to 2.18] vs. community: RR 1.53 [95% CI: 1.33 to 1.76]) (Chi^2 test for subgroup difference, p=0.00). There was no evidence that the relative effect of the intervention differed according to participant readiness-to-quit (meta regression, p=0.09). The subgroup of trials that included participants selected for motivation to change had a slightly larger effect estimate than the subgroup not selected for motivation, although the confidence intervals overlapped. Likewise, there was not an important difference in the effects of interventions delivered by cessation counseling specialists versus those provided by a nonspecialist health care provider, peer supporter, or lay health advisor (meta-regression, p=0.37). There was no clear evidence that increasing number of sessions or duration of personal contact had larger effects (bivariate meta regression, p=0.73). The subgroup of trials that offered eight or more sessions had the largest estimate (RR 2.10 [95% CI, 1.65 to 2.68])), but the confidence intervals overlapped for all four groups of interventions categorized by the number of sessions that included personal contact (i.e., 0 sessions, 1-3 sessions, 4-8 sessions, more than 8 sessions). Finally, there was no evidence of effect modification according to treatment uptake when comparing those with high (over 70% starting pharmacotherapy and receiving at least one session of support), moderate (over 30% starting pharmacotherapy and over 50% receiving at least one session of support), or low (less than 30% starting pharmacotherapy or less than 50% receiving at least one session of support) compliance with the intervention (Chi^2 test for subgroup difference, p=0.07).[127]

Pharmacotherapy Interventions

Nicotine Replacement Therapy

Primary Results

The most recent high-credibility review, conducted by Hartmann-Boyce (2018), systematically searched for evidence through July 2017 that compared NRT with placebo or no NRT control groups among adult smokers.[96] The review included 136 RCTs, 18 of which are new to this update, that ranged in size from fewer than 50 to over 8000 participants (median: 257). All six forms of NRT significantly increased the rate of cessation compared with placebo or no NRT, as did choice of NRT product (**Table 5**). Considering any form of NRT compared with placebo or no NRT, the pooled RR for abstinence was 1.55 (95% CI, 1.49 to 1.61; I^2=39%; k=133; n=64,640) at the longest followup (6 months or more). Overall, 16.9 percent of participants who received some type of NRT achieved abstinence at 6 months or longer (range 1.7% to 60.0%), compared with 10.5 percent of control participants (range 0.5% to 46.0%).

The review included trials among men or women, including six trials among pregnant women who smoked and were motivated to quit, irrespective of the setting from which they were recruited or their initial level of nicotine dependence. In most studies, participants were an average age of 40 to 50 years and the average number of cigarettes smoked was over 20 per day. Most studies took place in North America (k=62) and Europe (k=56) and included members of the community who volunteered in response to media advertisements and were treated in clinical settings. Twenty-six trials were conducted in a primary care or similar setting, with smokers typically recruited in response to a specific invitation from their doctor. The remaining trials were conducted in antenatal clinics, specialized smoking-cessation clinics, hospitals (in- or outpatient), drug abuse or psychiatric treatment centers, schools, or in settings designed to resemble over the counter (OTC) use of NRT.[96]

The primary analysis (i.e., the effectiveness of one or more types of NRT compared with a placebo or a control group receiving no NRT) consisted of 131 trials reporting 133 comparisons among 64,640 participants.[96] In this group of studies, 56 trials evaluated nicotine gum, 51 trials evaluated transdermal nicotine patches, 8 evaluated an oral nicotine tablet or lozenge, 7 evaluated a choice of products being offered, 4 evaluated intranasal nicotine spray, 4 evaluated nicotine inhaler, 2 evaluated the provision of patch and inhaler, 1 evaluated oral spray, and 1 each evaluated the provision of a patch and lozenge, patch and inhaler, and patch, gum, and lozenge. Most of the 56 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=51), 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=8), three trials used 2 mg sublingual tablets, one trial used a 1 mg lozenge, and two trials used 2 mg or 4 mg lozenges. All trials provided the same behavioral support in terms of advice, counseling, and number of followup visits to the active pharmacotherapy and

control groups, but different trials provided different amounts of support (in terms of number and duration of support).[96]

Evidence of Effect Modification

Indirect comparisons of trials within the Hartmann-Boyce review based on various study-, population-, intervention-, and outcome-related characteristics showed that the relative rates of abstinence were similar across groups.[96] For instance, there was no evidence that timing (12- vs. 6-months) or choice of outcome (continuous vs. point prevalence abstinence) produced different treatment effects among trials of nicotine gum or patch (there were too few trials to test these differences for other products). Likewise, there was no evidence of effect modification through indirect subgroup comparisons according to the intensity or type of behavioral support that was provided to the intervention and control groups. As expected, absolute quit rates among control groups varied according to the intensity of the behavioral support; for example, rates averaged 3.5 percent with low-intensity support, 9 percent with high-intensity individual support, and 11.7 percent with group-based support. In terms of setting, the pooled RRs according to subgroup were all similar, with overlap in the 95% confidence intervals. The pooled RR for trials of any form of NRT among community volunteers for whom care was provided in a medical setting was 1.62 (95% CI, 1.53 to 1.72; I^2=25%; k=6; n=24,957), similar to that of trials conducted in smoking clinics (RR 1.70 [95% CI, 1.48 to 1.96; I^2=0%; k=12; n=3300), in primary care settings (RR 1.50 [95% CI, 1.33 to 1.69]; I^2=0%; k=24; n=11,974), in hospitals (RR 1.39 [95% CI, 1.24 to 1.55]; I^2=15%; k=13; n=7037), and in settings similar to OTC (RR 1.40 [95% CI, 1.26 to 1.55; I^2=83%; k=9; n=13,163). Finally, there was no substantive change in the pooled effect estimate after a series of sensitivity analyses accounting for trial risk of bias (i.e., either excluding studies at high risk of bias or limiting the analysis to only those at low risk of bias) or study methods (i.e., removing studies with no biochemical verification or restricting to only placebo-controlled trials).[96]

Comparative Effectiveness of Different Doses, Duration, and Modes of NRT

A separate high-credibility review by Lindson (2019a) evaluated the effectiveness and safety of different forms, deliveries, doses, durations, and schedules of NRT for achieving smoking cessation.[104] The review included trials among people of any age who smoked and were motivated to quit, irrespective of the setting from which they were recruited or of their initial level of nicotine dependence. Any form of NRT was included, with eligible comparisons being any other form, dose, duration, or schedule of NRT use. Studies were not eligible if one of the study arms received an additional intervention component that could not be separated from the NRT intervention, making it impossible to establish whether any effect found was as a result of the difference in NRT use or the additional component.[104]

The review included 63 studies (n=41,509), 21 of which were new to this update.[104] The median sample size was 400 participants but ranged from 45 to 3575 participants. Most trials were among adult cigarette smokers with an average age of approximately 45 years old; six trials targeted specific populations including adolescents (1 trial), older adults (1 trial), men only (1 trial), those who were alcohol dependent or who had a history of alcohol dependence (2 trials), and adults with PTSD (1 trial). Trials typically recruited people who smoked at least 15

cigarettes per day; in most, the average number smoked was great than or equal to 20 cigarettes per day. Just about half of the studies (31/63, 49%) recruited participants directly from the community, typically in response to media advertisements, with the remaining trials mostly recruiting from referrals from clinicians or health care clinics including smoking cessation clinics or quitlines, substance abuse clinics, or primary care clinics.[104]

Fourteen studies compared the use of combination NRT (a fast-acting form plus a patch) with a single form of NRT and found that combination NRT resulted in higher long-term (6 months or longer) quit rates (RR 1.25 [95% CI, 1.15 to 1.36]; I^2=4%; k=14; n=11,356) (**Table 5**).[104] There was no evidence of subgroup differences when comparing combination therapy versus patch alone or a fast-acting form of NRT alone (Chi^2 test for subgroup difference, p=0.61). There was no evidence from direct comparisons that a higher dose patch of 42/44 mg or 21/25 mg patch was more effective than a lower dose patch of 21/22 mg patch or 14/15 mg. Five trials compared 4 mg to 2 mg gum use; overall, there was a statistically significant greater effect of the higher dose of gum on cessation; however, sensitivity analyses revealed that was only true among trials that were among high dependency smokers, with no evidence of an effect in low dependency smokers. Evidence from eight trials suggested that using either a form of fast-acting NRT or a patch resulted in similar quit rates at 6 months or more (RR 0.90 [95% CI, 0.77 to 1.05]; I^2=0%; k=8; n=3319). Nine trials compared the use of NRT or no NRT prior to the set quit date (i.e., "preloading" by using NRT while still smoking prior to an official quit date). The pooled effect found a positive statistically significant effect of NRT preloading on abstinence at 6 months or longer (RR, 1.25 [95% CI, 1.08 to 1.44]; I^2=0%; k=9; n=4395). No comparisons based on duration of combination therapy or patch therapy showed a statistically significant difference on smoking abstinence. Except for the comparison of combination versus single form NRT, these comparisons and findings are based on a relatively small number of trials and should be interpreted cautiously.[104]

Bupropion

Primary Results

The high-credibility Howes (2020) review included the most comprehensive evidence synthesis on the effectiveness of bupropion versus placebo or no pharmacotherapy.[98] The review included 87 studies that evaluated the effects of bupropion on smoking cessation and provided an analysis of 46 trials that evaluated smoking cessation after 6 months or more in those taking bupropion versus those taking a placebo or no pharmacotherapy. The pooled RR was 1.64 (95% CI, 1.52 to 1.77; k=46; n=17,866) with little evidence of heterogeneity (I^2=15%) (**Table 5**).[98] Within this analysis, most studies were based on continuous abstinence measures that were biochemically validated and were placebo controlled. Quit rates ranged from 3.7 to 43.5 percent (mean, 23.3%) among those receiving bupropion and from 0 to 32.8 percent (mean, 11.0%) among those in the control groups. Almost all included studies (45 of 46) randomized intervention participants to the recommended dose of bupropion at 300 mg daily (150 mg twice per day). Treatment duration ranged from 7 to 26 weeks.[98]

The Howes review assessed the effects of antidepressant medications, including bupropion, on smoking cessation rates at followup at least 6 months following initiation of treatment.[98]

Evidence related to other antidepressant medications, such as nortriptyline or citalopram, from the Howes review is discussed below under "Other Medications." For smoking cessation outcomes, the review required RCTs to compare bupropion with placebo or another nonbupropion control or compare different dosages of bupropion. The authors excluded trials in which all participants received the same bupropion treatment but different behavioral support. Most trials (75%) were conducted in North America. Forty-five (52%) of the 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 or NRT.[98]

Evidence of Effect Modification

In the review by Howes, the effects of bupropion were found to be similar regardless of the level of behavioral support offered.[98] None of the three studies that used factorial designs to compare the effects of bupropion with varying levels of behavioral support found evidence that the efficacy of bupropion varied between lower and higher levels of behavioral support or by type of counseling approach provided (i.e., individual-based cognitive behavioral therapy vs. group therapy). There was also no evidence of a differential effect of bupropion on cessation between subgroups depending on whether they participants were recruited specifically because they had a mental health disorder or they represented the general population. Additionally, four included studies – including the large EAGLES trial,[161] directly assessed whether there was any interaction between depression and cessation rates; none of these studies found evidence of effect modification.[98]

Varenicline

Primary Results

A 2016 moderate-credibility review by Cahill included 39 RCTs among adult smokers that evaluated the efficacy or safety of varenicline.[85] The review found that varenicline at standard doses more than doubled the chances of quitting compared with placebo. The pooled RR for validated continuous abstinence at 6 or more months' followup was 2.24 (95% CI, 2.06 to 2.43; I^2=60%; k=27; n=12,625) (**Table 5**). Quit rates ranged from 5.3 to 46.8 percent (mean, 25.6%) among those receiving varenicline and from 0 to 28.2 percent (mean, 11.1%) among those in the control groups.[85]

Just over half of the studies were conducted in the United States or were multisite and included settings in the United States or Canada.[85] The trials were conducted in smoking cessation clinics, hospitals, and universities and other research centers. None of the included studies took place in or involved primary care staff. Participants in most trials were adult smokers who were willing to make a quit attempt. Several trials were conducted in clinical subgroups, including among hospital inpatients and disease-specific subgroups (i.e., people with CVD, asthma, substance use disorder, depression, and bipolar/schizoaffective disorder).[85]

Most of the trials used the standard 12-week regimen of varenicline, routinely titrating the first week up to the recommended daily dose of 1 mg twice a day.[85] Three trials compared different dosage arms of varenicline against a placebo arm. Most trials compared varenicline with an identical placebo regimen; trials comparing varenicline with other pharmacotherapies are discussed below ("Comparative Effectiveness"). All trials provided brief counseling for quit support to both treatment and control groups. As a condition of inclusion, all the trials reported cessation at least 6 months from the start of the intervention. All the trials except one used biochemical verification of abstinence.[85]

Evidence of Effect Modification

There was no evidence of differences in the effects of varenicline according to different study, drug, and population characteristics in the review by Cahill.[85] A separate review by McKee (2016) found that varenicline versus placebo had a larger statistically significant effect size for women than men for continuous abstinence at both 3 and 6 months' followup (sex x medication interaction, $p<0.05$).[112] For example, at 6 months, varenicline increased the odds of quitting in women by 3.49 times (95% CI, 2.64 to 4.57) and by 2.59 times (95% CI, 2.20 to 3.06) in men, with the interaction demonstrating that varenicline was 31 percent more efficacious in women (OR, interaction for treatment condition by sex 1.31 [95% CI, 0.97 to 1.84; $p<0.05$). Equal efficacy was seen between men and women for both point prevalence abstinence and continuous abstinence at 1 year.[112]

Other Medications

In addition to the seven FDA-approved medications for smoking cessation (i.e., five forms of NRT, bupropion, and varenicline), various other antidepressants and nicotine receptor partial agonists have been evaluated for their effectiveness and safety in helping people stop smoking.

The review by Howes included a synthesis of the effectiveness of antidepressants including bupropion (discussed above), nortriptyline, selective serotonin reuptake inhibitors (SSRIs: fluoxetine, paroxetine, sertraline, citalopram and zimelidine), monoamine oxidase inhibitors (MAOIs: moclobemide, selegiline, lazabemide, EVT302), and other antidepressants (venlafaxine, St. John's wort, S-Adenosly-L-Methionine, doxepin, imipramine, tryptophan).[98] There was limited evidence for all comparisons, which prevents drawing robust conclusions about these therapies. A pooled analysis of six trials showed evidence of a significant benefit of nortriptyline versus placebo at 6 or more months followup (RR 2.03 [95% CI, 1.48 to 2.78]; I^2=16%; k=6; n=975). In contrast, none of the individual trials of SSRIs (k=7), MAOIs (k=6), or other antidepressants (k=4) showed a benefit on smoking cessation at 6 or more months followup nor did pooled estimates of these medications. Furthermore, comparing any of these other antidepressants as an adjunct to nicotine patch therapy versus nicotine patch alone did not show evidence of an additional benefit over NRT.[98]

In addition to synthesizing the evidence on varenicline (discussed above), the review by Cahill on nicotine receptor partial agonists included five trials testing the effects of cytisine (k=4, n=3461) to increase smoking abstinence.[85] The pooling two of the more recent trials of cytisine

found that more participants taking cytisine stopped smoking compared with placebo at 6 or more months' followup, with a pooled RR of 3.98 (95% CI, 2.01 to 7.87).[85]

Comparative Effectiveness of Different Pharmacotherapy Agents or Regimens

Comparison of Different Types of NRT

As noted above, no studies that compared fast-acting NRT with a nicotine patch found a differential effect on smoking cessation (RR 0.90 [95% CI, 0.77 to 1.05]; I^2=0%; k=8; n=3319).[104] One trial (n=1410) included in the Lindson review also compared participant- versus clinician-selected NRT and found no difference in quit rates at 6 months.[104]

Combination NRT vs. Single NRT

As stated above, combination NRT (i.e., the use of a fast-acting product and nicotine patch) was found to be superior to a single form of NRT in a pooled analysis of 14 direct comparisons (RR 1.25 [95% CI, 1.15 to 1.36]; I^2=4%; k=14; n=11,356) (**Table 5**).[104]

NRT vs. Bupropion

Howes included ten studies that directly compared bupropion with any form of NRT.[98] Pooled results did not detect a significant difference between the bupropion versus NRT (RR 0.99 [95% CI, 0.91 to 1.09]; I^2=18%, k=10; n=8230) (**Table 5**).[98]

NRT vs. Varenicline

Cahill and colleagues included eight trials that tested NRT against varenicline.[85] A pooled analysis of all of the trials indicated a benefit for varenicline over NRT at 6 months (RR 1.25 [95% CI, 1.14 to 1.37]; I^2=39%; k=8; n=6264) (**Table 5**). Removing three open-label trials (all at high risk of bias for blinding) slightly strengthened the effect estimate (RR 1.34 [95% CI, 1.19 to 1.50]) and increased the I^2 to 47%. In a separate review examining sex differences in the relative effectiveness of pharmacotherapy, the benefits of varenicline over NRT were greater for women than with men (RR for interaction effect, 1.19 [95% CI, 1.01 to 1.40).[124] In that review, women treated with varenicline were 41 percent more likely to achieve 6-month abstinence than women treated with NRT (RR 1.41 [95% CI, 1.12 to 1.76]). For men, the benefit of varenicline over NRT (16%) was smaller and not statistically significant (RR 1.16 [95% CI, 0.91 to 1.47]).[124]

NRT vs. Cytisine

One recent trial comparing cytisine with NRT in 1310 people found a benefit for cytisine at 6 months (RR 1.43 [95% CI, 1.13 to 1.80]).[85]

Bupropion vs. Varenicline

Six trials included in the Howes review directly compared the effects of bupropion versus varenicline on smoking cessation.[98] All six studies showed more favorable effects for varenicline

compared with bupropion, and all but one found these differences to be statistically significant. A pooled estimate of the six trials found that bupropion was less effective than varenicline (RR 0.71 [95% CI, 0.64 to 0.79]; I^2=0%; k=6; n=6286) (**Table 5**).[98] A separate review and network meta-analysis found greater effectiveness of varenicline versus bupropion in achieving 6-month abstinence among women (RR 1.38 [95% CI, 1.08 to 1.77]) versus men (RR 1.11 [95% CI, 0.85 to 1.45] (RR for interaction effect, 1.22 [95% CI, 1.02 to 1.47]).[124]

Bupropion Plus NRT vs. NRT

A pooled estimate of 12 studies that directly compared the addition of bupropion 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]; I^2=52%; k=12; n=3487), although studies were clinically and statistically heterogeneous.[98]

NRT Plus Varenicline vs. Varenicline

A review by Chang and colleagues (2015) included three RCTs with 904 participants that compared combined varenicline and NRT therapy with varenicline alone.[87] Only two of the trials reported continuous smoking abstinence at 6 months. Both trials showed a favorable effect of combination therapy, although only one reached statistical significance.[87]

Bupropion Plus Varenicline vs. Varenicline

In the Howes review, there was no evidence that combination bupropion and varenicline resulted in higher smoking cessation rates than varenicline alone (RR 1.21 [95% CI, 0.95 to 1.55]; I^2=15%; k=3; n=1057).[98]

Support for Medication Adherence

Finally, a 2019 review by Hollands assessed the effectiveness of interventions that aimed to increase adherence to medications for smoking cessation.[97] The review included 10 studies, all of which reported the effects of the intervention on adherence outcomes. There was some evidence that interventions that devote special attention to improving adherence through the provision of information and facilitation of problem-solving can lead to modest increases in adherence, when added to behavioral support for smoking cessation. Five studies also reported on the effects of the adherence intervention on abstinence at 6 months or greater, with evidence of no effect on smoking abstinence (RR 1.16 [95% CI 0.96 to 1.40]; I^2=48%; k=10; n=3593) (**Table 5**).[97]

Behavioral Interventions

Behavioral Support as an Adjunct to Pharmacotherapy

Primary Results

The high-credibility review by Hartmann-Boyce (2018) assessed the effect of increasing the

intensity or changing the content of behavioral support among smokers using smoking cessation medications.[95] The review included RCTs in which adult smokers in both the intervention and control conditions received pharmacotherapy for smoking cessation, but they differed by the amount or content of behavioral support. Participants in the control condition received less-intensive behavioral support than participants in the intervention condition, often limited to written information alone, or a different approach to behavioral support but matched for contact time.[95]

Eighty-three studies were included, of which 36 are new for this update.[95] Over 29,000 participants are represented in the included study arms, with a range of 30 to 4614 participants in the individual trials. A meta-analysis of 65 trials suggested that increasing the intensity of behavioral support for smokers making a cessation attempt with the aid of pharmacotherapy typically leads to a relatively small increase in the proportion who have quit at 6 to 12 months. The estimated RR was 1.15 (95% CI, 1.08 to 1.22; I^2=8%; k=65; n=23,331) (**Table 5**). The average absolute quit rate of both the intervention (20%) and control groups (17%) were quite high and were comparable to the intervention groups in the trials of pharmacotherapy versus placebo. While most studies reported point prevalence abstinence instead of continuous or prolonged abstinence, the review found no difference in the relative effect between studies that reported point prevalence rather than continuous abstinence at 12 months.[95]

Twenty-nine studies (35%) recruited people in a health care setting (excluding smoking cessation clinics), including 10 studies that took place in primary care.[95] Since the intervention included the provision of pharmacotherapy, most of the studies recruiting in a health care setting enlisted volunteers who were interested in making a quit attempt, although motivation to quit was not always an explicit eligibility criterion. The remaining studies recruited community volunteers interested in quitting.[95]

Most studies offered NRT, specifically the nicotine patch.[95] Seven studies provided bupropion alone, one provided nortriptyline alone, and four provided varenicline alone. The remaining studies offered participants a choice or combination of medications. The intensity of the behavioral support, in both the number of sessions and their duration, was very heterogeneous for both the intervention and control arms. In seven studies, the controls received no counseling. In 30 studies, the control arms had one to three contacts (either face-to-face or by telephone), and most of these had a total contact duration of 4 to 30 minutes. In 34 studies the control group was scheduled to receive four to eight contacts, with most involving a total contact duration of over 90 minutes. The 12 remaining studies scheduled over eight contacts for the controls. Typically, the intervention involved only a little more contact than the control, so that the least intensive control conditions were in trials with only moderate-intensity interventions.[95]

Evidence of Effect Modification

The effect was similar and statistically significant for the subgroup of studies that examined behavioral support as an adjunct to NRT (k=50) and bupropion (k=5) specifically.[95] Results of the remaining trials among smokers using other pharmacotherapies (e.g., varenicline) or a choice of pharmacotherapy were generally not statistically significant, although there were few trials in these subgroups and a test for difference between subgroups was not significant. There was little

evidence of any dose-response effect according to the number of contacts in the intervention and control groups (and the contrast between those groups), although the point estimate was highest for the subgroup in which controls did not have any personal contact (RR 1.20 [95% CI, 1.02 to 1.43]). Seventeen studies, all new to this update, compared interventions matched for contact time but provided through different modalities, providing different content, or employing different behavior change techniques. All studies in this group employed different comparisons and were not pooled. Only one trial – comparing motivational interviewing with health education – found a statistically significant difference between the two interventions, with the finding in favor of health education.[95]

Physician Advice

Primary Results

The high-credibility review by Stead (2013b) summarized evidence from 42 trials on the effectiveness of physician advice in promoting smoking cessation published through January 2013.[125] 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. Advice was defined as verbal instructions from the physician with a "stop smoking" message regardless of whether information was provided about the harmful effects of smoking. In a meta-analysis, 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=26; n=22,239) (**Table 5**). Absolute quit rates ranged from 1 to 23 percent among intervention participants (mean: 8.0%), and from 1 to 14 percent among control participants (mean: 4.8%).[125]

Evidence of Effect Modification

The results of the main meta-analyses were not sensitive to exclusion of trials at high risk of bias for any item.[125] When stratified by intervention intensity, both brief advice (single consultation lasting less than 20 minutes plus up to one followup visit) (RR 1.66 [95% CI, 1.42 to 1.94]) and intensive advice (greater time commitment at the initial consultation, use of additional materials beyond a brochure, or more than one followup visit) (RR 1.86 [95% CI, 1.60 to 2.15]) 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). However, direct comparisons 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 without smoking-related disease (10 studies), but the effect might be larger when the intervention is provided to smokers in high-risk groups (e.g., those with heart disease, chronic obstructive pulmonary disease) (based on only 5 trials).[125]

An 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).[125] 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.[125]

Nurse Advice

Primary Results

A more recent high-credibility review by Rice (2017) synthesized the evidence on nursing interventions for smoking cessation.[119] Similar to the review of physician advice, included nursing interventions consisted of 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" but defined intervention intensity slightly differently. In the Rice review, low-intensity interventions were those that were conducted during a single consultation lasting 10 minutes or less, with up to one followup visit (as opposed to 20 minutes in the physician advice review) and high-intensity interventions as those in which 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.[119]

The Rice review included 58 trials, nine of which are new to this update.[119] Twenty-eight trials (48%) recruited from primary care or outpatient settings, and another 22 trials (38%) intervened with hospitalized patients. The remaining trials recruited from workplaces, communities, universities, and other sites. Just under half of the trials recruited individuals with chronic diseases (e.g., cardiovascular disease, respiratory disease, diabetes) or hospitalized patients. Most trials (k=44) compared a nursing intervention to a usual care or minimal intervention control and contributed to the primary meta-analysis. The remaining comparisons were made between two nursing interventions that involved different components or a different number of contacts (k=11) or were excluded from meta-analyses because of incomplete data (k=6). The estimated pooled RR comparing smoking cessation support provided by a nurse with usual care or minimal intervention was 1.29 (95% CI, 1.21 to 1.38; I^2=50%; k=44; n=20,881) (**Table 5**).[119]

Evidence of Effect Modification

There was no evidence of different effects among interventions classified as low- versus high-intensity (Chi^2 test for subgroup difference, p=0.87).[119]

Individual Behavioral Counseling

Main Results

We identified one recent high-credibility review by Lancaster (2017) that reviewed the evidence on individual counseling in promoting smoking cessation.[103] The review included studies among nonpregnant smokers that tested the effect of an individual counseling intervention compared with no treatment, brief advice, self-help materials, or a less intense individual counseling intervention. Individual counseling was defined as a face-to-face encounter between a smoker

and a counselor trained in providing smoking cessation assistance. Studies of counseling delivered by physicians or nurses, those that combined counseling with pharmacotherapy, and those using motivational interviewing were excluded given their inclusion in other relevant reviews (which are all included in this overview of reviews). Forty-nine trials were included, with around 19,000 participants. Thirty-three studies contribute to the primary analysis comparing individual counseling with a minimal-contact behavioral intervention. Eleven studies compared different intensities of interventions, and five compared counseling approaches that were similar in intensity of contact. The recruitment settings and study populations were highly variable and included those recruited as medical or surgical inpatients or outpatients, at primary care clinics and worksites, and as community volunteers. The counseling intervention typically included a review of a participant's smoking history and motivation to quit, help in identification of high-risk situations, and the generation of problem-solving strategies to deal with such situations. Some studies also provided additional components such as written materials or videos. The therapists who providing the counseling were generally described as smoking cessation counselors with professional backgrounds in social work, psychology, psychiatry, health education, and nursing.[103]

The pooled effect size based on 33 studies demonstrated statistically significant benefit of individual counseling compared with a minimal contact control (RR 1.48 [95% CI, 1.34 to 1.64]; I^2=46%; k=33; n=13,762) (**Table 5**).[103] In these studies, a minimal contact control ranged from usual care to up to 15 minutes of advice, with or without the provision of self-help materials. Most of the interventions implemented multiple sessions of face-to-face support in addition to telephone contact. Within this group of studies, six trials included pharmacotherapy for both arms. The effect estimate was higher in the subgroup of studies when pharmacotherapy was not provided (RR 1.57 [95% CI, 1.40 to 1.77]; I^2=50%; k=27; n=11,100) than in the studies testing the additional effect of counseling when participants had access to pharmacotherapy (RR 1.24 [95% CI, 1.01 to 1.51]; I^2=0%; k=6; n=2662) and the test for a subgroup difference was statistically significant (Chi^2 test for subgroup difference, p=0.04). There was some evidence that more intensive versus less intensive counseling resulted in greater cessation (16.8% vs. 12.7% absolute quit rates, respectively) (RR 1.29 [95% CI, 1.09 to 1.53]; I^2=48%; k=8; n=2920), and there was a difference in this effect according to whether pharmacotherapy was also provided (Chi^2 test for subgroup difference, p=0.04). There was limited evidence from studies comparing different types of individual counseling.[103]

Group Behavioral Therapy

Primary Results

The moderate-credibility review by Stead (2017) synthesized the evidence on the effect of group-delivered behavioral interventions in achieving long-term (6 months or more) smoking cessation among nonpregnant adult smokers.[126] Included interventions were those in which smokers attended scheduled meetings and received some form of behavioral intervention, such as information, advice, and encouragement or cognitive behavioral therapy delivered over at least two sessions. The review included 66 trials, 44 of which compared a group program with a non-group-based cessation intervention or a no-intervention control. The remaining 22 did not have a non-group control and only contributed to comparisons between different group-based

programs. Most studies recruited community volunteers prepared to participate in group programs; only three recruited from primary care. The group programs varied in length, format, and content. Most programs offered six to eight sessions, with the first few sessions devoted to motivation for quitting, health benefits, and strategies for planning a quit attempt. Compared with non-group self-help programs, group-based therapy interventions resulted in a statistically significant increased risk of quitting tobacco at 6 or more months' followup (RR 1.88 [95% CI, 1.52 to 2.33]; I^2=0; k=13; n=4395) (**Table 5**). A separate analysis of 14 trials found a small benefit of group support compared with brief support from a physician, nurse, or pharmacist with a conference interval just excluding no effect (RR 1.22 [95% CI, 1.03 to 1.43]; I^2=59%; k=14; n=7286). When combining the results of five trials (n=1523) that examined group therapy as an adjunct to pharmacotherapy, the analysis did not detect a statistically significant increased quit rate for combined therapy over pharmacotherapy without group support. Similarly, there was no evidence, based on six trials (n=980), that group therapy was more effective than individual therapy when the number of sessions were matched.[126]

Motivational Interviewing

Primary Results

A 2019 high-credibility review by Lindson (2019b) reviewed the evidence on the effectiveness of motivational interviewing (MI) to increase smoking cessation.[106] In this review, RCTs conducted among nonpregnant smokers with an MI intervention were included. The intervention must have been based on the MI principles as defined by Miller and Rollnick,[162] making explicit reference to at least some MI principles: exploration of ambivalence, decision balance, assessment of motivation and confidence to quit, elicitation of "change talk," and support for self-efficacy and in the opinion of the review authors, complied with these principles and practices. The review identified 37 trials, involving over 15,000 participants. The included MI interventions were conducted in one to 12 sessions, with the total duration of MI ranging from 5 to 315 minutes. Interventions were primarily delivered by primary care physicians, nurses, or counselors. Pooling studies that compared a smoking cessation intervention supplemented by MI with the same smoking cessation intervention without MI suggested a small potential benefit of MI; however, the 95% CI spanned one and there was moderate heterogeneity detected (RR 1.07 [95% CI, 0.85 to 1.36]; k=12; n=4167; I^2=47%) (**Table 5**). Nineteen trials compared an MI intervention to another type of smoking cessation intervention. The point estimate was in favor of MI; however, the confidence intervals were consistent with substantial benefit and with potential harm (RR 1.24 [95% CI, 0.91 to 1.69]; k=19; n=5192; I^2=54%). Furthermore, there was no evidence of a benefit of a MI smoking cessation intervention when compared with no intervention within four trials.[106]

Evidence of Effect Modification

There was no clear evidence to suggest that the effect of MI was moderated by the intervention provider participants' motivation to quit at baseline, whether MI was delivered face-to-face, or whether MI fidelity monitoring took place.[106] Five trials directly compared the effectiveness of more intensive versus less intensive MI intervention. There was some suggestion that more intensive interventions were associated with greater smoking abstinence; however, this analysis

included several studies at high risk-of-bias and removing those studies produced a nonsignificant result.[106]

Decision Aids

Primary Results

A 2018 moderate-credibility review by Moyo synthesized the evidence on the effectiveness of decision aids for smoking cessation in adults.[115] Both experimental and quasi-experimental studies that evaluated the use of decision aids to promote shared decision making between a patient and healthcare provider were included. For the purpose of this review, a decision aid was defined as a tool any healthcare provider used to share with and inform people about treatment options, including the risks, and costs and benefits of potential choices. Any form of decision aid was included such as pamphlets, brochures, cards, DVDs, or web-based applications. The review identified seven studies that met eligibility criteria with decision aids including web- or computer-based aids (3 studies), a video decision aid (1 study), a print-based aid (2 studies), and a video plus print decision aid (1 study). The decision aids were delivered by a healthcare provider in only two cases. The other studies all evaluated a decision aid where provider followup was optional based on the participant's decision after use of the aid. Of the six studies that measured abstinence, only two suggested a benefit of using a decision aid (versus usual care) on smoking abstinence and only one was statistically significant.[115]

Print-Based Self-Help Materials

Primary Results

A recent updated moderate-credibility review by Livingstone-Banks (2019b) assessed the effectiveness of different forms of print-based self-help materials compared with no treatment or other minimal intervention strategies.[109] The review included 75 studies, with only 3 of them new to this update. Self-help interventions were defined as any manual or program designed to be used by individuals to assist a quit attempt not aided by health professionals, counselors, or group support. For the most part, that included written materials such as booklets and leaflets/brochures, but information could also have been provided via audio, video, or a similar medium. Brief leaflets on the health effects of smoking were considered a control condition if they were compared with a more substantial print-based intervention. Interventions that included a single face-to-face session for the purpose of supplying the print-based materials were included, but interventions that provided repeated sessions of advice in addition to self-help materials were excluded. Additionally, interventions delivered via a computer or mobile phone as well as those that included telephone counseling as adjuncts to self-help materials were excluded because these interventions were covered in other published reviews (which are also included in this overview of reviews).[109]

The content and format of the self-help programs varied.[109] The most frequently used materials were the American Lung Association's cessation manual: *Freedom From Smoking in 20 Days,* and the maintenance manual: *A Lifetime of Freedom From Smoking*.[163] Most other programs were not named or fully described. Most of the recent studies used computerized expert systems

to provide tailored materials judged to be relevant to the characteristics of each smoker, based on baseline data.[109]

Overall, after pooling 32 studies of non-tailored self-help materials compared with no self-help, irrespective of the level of contact and support common between groups, the point estimate showed a small, but not statistically significant, benefit of the intervention (RR 1.06 [95% CI, 0.95 to 1.19]; I^2=25%; k=32; n=28,451) (**Table 5**).[109] Trials varied considerably in ways that could potentially impact results, such as whether the materials were tailored, and the amount of face-to-face advice or counseling provided to both the intervention and control groups.[109]

Evidence of Effect Modification

When isolated to only studies that compared groups who received self-materials versus groups who received *no* intervention at all, results were statistically significant: a meta-analysis of 11 trials that provided standard non-tailored self-help manuals or materials compared with no materials for the control group showed some benefit of self-help materials, although the confidence interval only narrowly excluded 1.0 (RR 1.19 [95% CI, 1.03 to 1.37]; I^2=0%; k=11; n=13,241).[109] Relative effects were also larger when comparing the subset of studies in which participants in the intervention group received *tailored* self-help materials versus controls receiving no intervention (RR 1.34 [95% CI, 1.19 to 1.51]; I^2=0%; k=10; n=14,359). However, there was no evidence that tailored materials were superior to nontailored materials in indirect or direct comparisons.[109]

Telephone Counseling and Support

Primary Results

A recent moderate-credibility review by Matkin (2019) evaluated the effects of telephone support to help smokers quit.[110] Included trials evaluated the impact of proactive (i.e., recruiter-initiated contact) and reactive (i.e., smoker-initiated contact) among smokers of any age, including pregnant individuals. The review identified 104 trials (30 of which are new to this update) including 111,653 participants that met inclusion criteria. All included trials were relatively large, with a median sample size of 735 and only 7 trials with a sample size of less than 100. Participants were mostly adult smokers from the general population, but some studies included adolescents, pregnant women, and people with long-term or mental health conditions. Most studies (100/104) assessed proactive telephone counseling programs as opposed to reactive forms. Proactive telephone counseling interventions included: 1) additional counseling calls that took place following smokers calls to helplines and 2) counseling calls from counselors or other health care providers that were among samples of smokers who had not originally contacted a help line (essentially a “cold call”). Some studies provided telephone counseling alone, but many others provided telephone counseling along with minimal support such as self-help materials, or more active support such as face-to-face counseling, or with medications. The number of calls ranged from a single call to 12 calls. The duration of the calls was typically 10 to 20 minutes, although the first calls were often longer. Counseling was most often provided by professional counselors or trained health care professionals.[110]

Among trials including smokers who contacted helplines, quit rates were higher for smokers receiving multiple additional telephone counseling sessions (mean quit rate, 10.8%) compared with a control condition that was provided self-help materials or brief counseling in a single call (mean quit rate, 7.8%) (RR 1.38 [95% CI, 1.19 to 1.61]; I^2=72%; k=14; n=32,484) (**Table 5**).[110] Likewise, in studies that recruited smokers who did not call a helpline, telephone counseling increased quit rates (mean quit rate, 13.9%) modestly compared with other minimal or brief counseling control groups (mean quit rate, 11.0%) (RR 1.25 [95% CI, 1.15 to 1.35]; I^2=52%; k=65; n=41,233) (**Table 5**). In both instances, however, statistical heterogeneity was moderate to substantial. Only three included studies assessed the impact of offering reactive counseling by providing access to a helpline/quitline, compared with not being provided access with only one finding a statistically significant increased rate of quitting among those with helpline access. Both proactive and reactive telephone counseling appeared to increase quit rates compared with health care provider counseling, but this finding is limited by the small number of trials testing this comparison (four trials).[110]

Evidence of Effect Modification

The exclusion of trials among pregnant women, adolescents, and those at high risk of bias did not have a large influence on the effect size or statistical heterogeneity in the review.[110] Likewise, subgroup analyses based on the baseline support provided to both intervention and control groups, counseling intensity, or motivation did not fully explain the heterogeneity in the results. However, there was some evidence through multivariate meta regression that the baseline support offered to both treatment arms as well as whether participants were selected for motivation to quit may have had some influence on the effect size related to proactive telephone counseling for smokers who did not call quitlines. The relative difference was greater for those receiving adjunctive self-help materials (35% greater) or brief face-to-face counseling (37% greater) than pharmacotherapy (referent). In the same model, studies that selected participants because of their motivation to quit were associated with a 26 percent increased relative risk compared with studies that did not select participants based on their motivation to quit. There was not enough evidence to suggest that a higher number of calls would result in a larger effect, although there was limited evidence that offering 3 to 6 calls may be more effective than offering just one single proactive call.[110]

Mobile Phone-Based Support

Primary Results

The high-credibility review by Whittaker (2019) identified 26 RCTs 14 of which are new) (n=33,849) that included an evaluation of a mobile phone-based intervention.[138] The review included interventions that were aimed at mobile phone users, were based on delivery via mobile phone, or used any functions or applications that could be used or sent via a mobile phone. The review excluded trials that used mobile phones as an adjunct to face-to-face or internet-based programs or that could not separate the effects of the mobile phone intervention components from the effects of a multicomponent intervention. All studies tested automated text messaging interventions (SMS) as a central component of the intervention. Several studies paired SMS with in-person visits, although the majority were purely test-messaging interventions. Five studies

tested the effectiveness of smoking cessation smartphone apps alone, although the apps varied considerably in intervention content and components. Trials represented both young adults (mean age 18–27 years) and middle-age adults (up to mean age of 45 years).[138]

A meta-analysis of 13 studies that compared a text messaging intervention with minimal smoking cessation support showed a positive benefit of text messaging interventions on smoking cessation at 6 months' followup (RR 1.54 [95% CI, 1.19 to 2.00]; I^2=71%; k=13; n=14,133) (**Table 5**) with the average absolute quit rates of 9.5 percent versus 5.6 percent in the intervention versus control groups, respectively.[138] A similar effect was found when comparing mobile phone-based interventions with no intervention (RR 1.59 [95% CI, 1.09 to 2.33]; I^2=0%; k=4; n=997).[138]

Evidence of Effect Modification

The review found minimal differences in the overall result when pooled subgroups of studies were based on frequency of text messages (high-frequency vs. low-frequency), text message-only interventions, or those with only minimal (versus active) controls.[138]

Real-Time Video Counseling

Primary Results

A new high-quality review by Tzelepis (2019) assessed the effectiveness of real-time video counseling delivered individually or to a group (e.g., via video communication software such as Skype and FaceTime) in increased smoking cessation.[134] Only two trials were identified (n=615). Both studies delivered real-time video counseling for smoking cessation individually, compared with telephone counseling. There was no statistically significant tretement effect for smoking cessation across the two included studies (RR 2.15 [95% CI, 0.38 to 12.04]; I^2=66%; k=2; n=608) (**Table 5**).[134]

Internet-Based Support

Primary Results

An updated high-credibility review by Taylor (2017) was designed to determine the effectiveness of internet-based interventions for smoking cessation and to evaluate whether intervention effectiveness was altered by tailoring interactive features, and if there was a difference in effectiveness between adolescents, young adults, and adults.[129] Any type of internet intervention was eligible, and the comparison could be a no-intervention control, a different internet intervention, or a non-internet intervention. The review identified 67 RCTs, including data from over 110,000 participants. Thirty-nine of the trials were new to this update. Most of the studies were among adults; three studies recruited adolescents only and seven studies recruited young adults or university or college students. Most studies were conducted in the United States and recruitment and all intervention components were Web-based, with participants finding the sites through search engines and browsing. As a result of the recruitment methods, participants in

these trials were motivated to quit smoking and chose the internet as a tool for smoking cessation support. Sample sizes ranged from fewer than 70 to nearly 12,000.[129]

A range of internet interventions was 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.[129] Many interventions provided tailored interventions but differed substantially in the amount of tailoring. Some trials also included counseling or support from nurses, peer coaches, or tobacco treatment specialists. Some of the more recent trials incorporated online social networks such as Facebook, Twitter, and online forums. In 15 trials, all participants were using, or were offered, pharmacotherapy and the internet component was thus evaluated as an adjunct to pharmacotherapy. Nine trials of lifestyle interventions provided content on a range of topics, including smoking cessation. These trials were not included in the main synthesis and meta-analysis given that results were not isolated for smokers only.[129]

Given the heterogeneity of the included evidence in terms of the interventions (i.e., tailored vs. not, interactive vs. not) and control conditions (i.e., nonactive controls [printed self-help guides, usual care], active controls [telephone, face-to-face counseling], addition of an internet program plus behavioral support, or comparing one internet intervention with another), the results were synthesized into distinct subgroups.[129] Compared with a nonactive control group, pooled results demonstrated an effect in favor of interactive and tailored internet-based interventions (RR 1.15 [95% CI, 1.01 to 1.30]; I^2=58%; k=8, n=6786) (**Table 5**). However, these results should be interpreted with caution, as statistical heterogeneity was high and was unexplained despite perceived clinical homogeneity. Furthermore, though the pooled effect was in the direction of potential benefit, this analysis was based on a fixed effect model which can result in substantially different results compared with a random effect model when there are big imbalances in sample sizes in the studies being pooled. In fact, in this analysis, average absolute quit rates were slightly *lower* for the intervention (12.8%) vs. control (12.9%) groups. Five studies evaluated an internet intervention plus behavioral therapy compared with a nonactive control and indicated a collective positive effect on the intervention (RR 1.69 [95% CI, 1.30 to 2.18]; k=5; n=2334), although again, the statistical heterogeneity was quite high (I^2=60%).[129]

Evidence of Effect Modification

Given the heterogeneity in the included interventions and comparators, the review analyzed studies within distinct groups (interactive and tailored internet-based interventions, interactive but not tailored internet-based interventions, and neither interactive nor tailored internet-based interventions).[129] When compared with a nonactive control group, in all cases, statistical heterogeneity was high and unexplained; although the review performed no further analyses to explain this heterogeneity (likely due to largely null effects). In direct comparisons, none of the studies comparing an Internet intervention or Internet intervention plus behavioral support with an active control detected statistically significant evidence for differences between the conditions. Seven studies compared an interactive and/or tailored internet program or website with an internet intervention that was neither tailored nor interactive. Pooled results favored the intervention group; however, they were not statistically significant (RR 1.10 [95% CI, 0.99 to 1.22]; I^2=0%; k=7; n=14,623).[129]

Incentives

Primary Results

We included one high-credibility review by Notley (2019) that examined whether incentives and contingency management programs led to higher long-term quit rates among smokers.[116] Thirty-three studies among adults met inclusion criteria, including over 21,600 participants. Nearly three-quarters of the trials (22/33) took place in the United States. The incentives included cash rewards or monetary incentives in the form of vouchers, prize drawings alongside a guaranteed reward, the recovery of money deposited by those taking part, or a combination of incentive types. Seven studies included complex payment schedules that specifically rewarded continuous abstinence. The total financial amount of incentives (where reported) varied considerably between trials, from zero (self-deposits) to a range between $45 and $1,185. All but one study included additional cessation support such as brief advice, pharmacotherapy, and in one case – e-cigarettes. Most of the studies took place in worksites or substance misuse clinics; six studies delivered support in a health clinic including mental health clinics, head and neck cancer clinics, or primary care clinics. The pooled RR for quitting with incentives at longest followup (6 months or more) compared with usual care or a non-incentive-based intervention was 1.49 ([95% CI, 1.28 to 1.73]; I^2=33%; k=30; n=20,097) (**Table 5**).[116]

Evidence of Effect Modification

There was no significant difference between studies that offered incentives up until the point of measuring abstinence (i.e., at 6 months) versus those where the longest followup occurred after the incentive schedule had ended.[116] In the subgroup of studies in which followup was beyond the provision of incentives a statistically significant benefit was found, suggesting that the impact of incentives continues for a least some time after incentives are no longer provided. The results of an exploratory meta-regression suggested that there was no clear direction of effect between trials offering low or high total value of incentives. Two studies conducted a head-to-head comparison between a rewards-based and deposit-refund-based approach and found both to be effective with no significant differences or negligible differences between groups.[116]

Biomedical Risk Assessment

Primary Results

We identified one moderate-credibility review, Clair (2019), that evaluated the efficacy of biomedical risk assessment (with or without other behavioral counseling) to aid in smoking cessation.[88] Biomedical risk assessment interventions included a physical measurement to increase motivation to quit smoking, such as exhaled carbon monoxide (CO), spirometry, atherosclerotic plaque imaging, and genetic testing. The review identified 20 studies, 5 of which are new to this update, that met inclusion criteria. These trials represented over 9000 participants, with studies ranging from 64 to 2110 participants per study. In most studies, the biomedical testing component was added to intensive quit-smoking sessions (which both the intervention and control groups received), with counseling lasting up to 60 minutes and complemented by written material and reinforcement sessions or followup phone calls.[88]

Five studies tested feedback on smoking exposure, each measuring the effect of exhaled CO measurements; there was no evidence of a statistically significant benefit from these studies in pooled analysis (RR 1.00 [95% CI, 0.83 to 1.21]; I^2=0%; k=5; n=2368) (**Table 5**).[88] Likewise, there was no evidence of a significant benefit of interventions providing feedback on participants' genetic susceptibility to smoking-related cancer or Crohn's disease (RR 0.80 [95% CI 0.63 to 1.10]; I^2=0%; k=5; n=2064). Eleven studies provided feedback on smoking-related harm: four tested the combination of exhaled CO measurement and spirometry, five tested the effect of spirometry alone or with the addition of feedback on lung age; and two tested the effect of undergoing an ultrasonography of carotid arteries and/or femoral arteries with photographic demonstration of atherosclerotic plaques when present. A pooled analysis of all 11 studies resulted in an unclear effect on smoking cessation (RR 1.26 [95% CI, 0.99 to 1.61]; I^2=34%; k=11; n=3314).[88]

Evidence of Effect Modification

There was no evidence that the effectiveness of these interventions differed according to the type of biomedical feedback given (i.e., smoking exposure risk, smoking-related disease risk, or smoking-related harm).[88]

Exercise

Primary Results

We included one high-credibility review by Ussher (2019) that evaluated the effect of exercise on smoking cessation (n=7,279).[135] The review included RCTs that compared an exercise program alone, or an exercise program as an adjunct to another smoker cessation program, with a cessation program alone or another non-exercise control group among adult smokers who were motivated to quit. Trials among adolescents as well as persons with psychological health conditions were excluded. The review included 24 trials that met inclusion criteria; six new studies were identified since the last review on this subject. Most of the trials used supervised, group-based aerobic exercise intervention supplemented by home-based exercise. In most cases, the exercise intervention started before the stated quit date. Twenty-two studies included smoking cessation support as the comparator, and two studies had relapse prevention support as the comparator, with all but one study offering this support for both exercise and control groups. The sample size in these trials was smaller than that seen in other smoking cessation trials, ranging from 20 to 2318, with more than half of the studies enrolling fewer than 100 participants.[135]

In pooled analyses, there was no statistically significant difference between smoking cessation interventions that included exercise versus those that did not (RR 1.08 [95% CI, 0.96 to 1.22]; I^2=0%; k=21; n=6607) at 6 or more months' followup **(Table 5**).[135]

Evidence of Effect Modification

There was no evidence in the review that the effects differed according to whether the exercise included aerobic exercise, resistance training combined modalities, or unknown types of physical

activity.[135] None of the effects were statistically significant among these subgroups by exercise type, and the confidence intervals of pooled analyses and individual effects all overlapped. Excluding studies among special populations such as those with mental health issues, or pregnant populations did not affect the interpretation of the results.[135]

Complementary and Alternative Therapies

Primary Results

We included two reviews that examined the effectiveness of complementary and alternative therapies on smoking cessation, one on acupuncture and acupressure[137] and one on hypnotherapy.[82] The high-credibility review on acupuncture, by White (2014), included 38 RCTs that compared the effects of acupuncture (23 studies), acupressure (5 studies), laser therapy (3 studies), and electrostimulation (7 studies) versus no or sham intervention for smoking cessation at short-term (6 weeks or less) and long-term (6–12 months) followup.[137] 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 5**). Similarly, there was no evidence of a benefit of acupressure, continuous auricular stimulation, or electrostimulation versus sham interventions on long-term cessation.[137]

The high-credibility review on hypnotherapy, by Barnes (2019), included 14 trials.[82] 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., no intervention, attention-matched behavioral interventions, brief behavioral interventions, intensive behavioral interventions, rapid/focused smoking, drug, and placebo). The studies varied greatly in the method of hypnotic induction and the number and duration of hypnotherapy sessions. 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 **(Table 5**). In the group with the most trials, there was no overall difference in smoking cessation rates between groups at 6 months or greater followup between hypnotherapy versus attention-matched smoking cessation behavioral intervention (RR 1.21 [95% CI, 0.91 to 1.61]; k=6; n=957; I^2=36%).[82]

Systems-Level Interventions

Primary Results

We included two reviews that addressed the effectiveness of system-level interventions to support smoking cessation.[84, 130] The reviews contained mutually exclusive bodies of evidence given differences in scope. The first high-credibility review, by Boyle (2014), focused on the effectiveness of electronic health record (EHR)-facilitated interventions on smoking cessation support actions by clinicians, clinics, and health care delivery systems.[84] The most common enhancement of the EHR was connecting smoking patients with a telephone-based quitline. While the review included 16 studies (6 group RCTs, 1 individual RCT, and 9 nonrandomized observational studies), none of the studies included a direct assessment of patient quit rates

(**Table 5**). One group RCT (n=9589) reported a comparison of quit rates between intervention and control clinics that were measured indirectly based on EHR documentation of smoking status. In that study, significantly more smokers in the intervention clinics were subsequently documented as nonsmokers compared with smokers in the control clinics 6 months after changes were implemented (5.3% vs. 1.9%, p<0.001). The remaining studies focused on the impact of EHR changes on smoking support actions by clinicians, clinics, and health systems and specifically focused on the 5 A's (*Ask, Advise, Assess, Assist, Arrange*). In general, most studies found an increase in the documentation of tobacco use and quit assistance following the introduction of an electronic reminder.[84]

The other high-credibility review, by Thomas (2017), was more broadly scoped and focused on the effectiveness of practice and policy changes within organizations to integrate the identification of smokers and the subsequent offering of evidence-based nicotine dependence treatments into usual care, beyond just changes to the EHR.[130] The review included seven group RCTs, of which all but one was conducted in the United States. The settings included primary care clinics (2 trials), dental clinics (2 trials), a community pharmacy (1 trial), VA medical center (1 trial), and a pediatric practice focused on parents (1 trial). Interventions were characterized based on the provision of six system change components: 1) identification/documentation of smoking status, 2) smoking cessation training/resources/feedback for providers, 3) dedicated staff to support cessation activities, 4) policies to improve access to cessation interventions, 5) free smoking cessation treatment from the organization, and 6) reimbursement of clinics for providing smoking cessation support. None of studies incorporated all six system change strategies. The identification of all smokers and training staff and provision of evidence-based treatment were components of all seven included studies. All included studies used the services of existing staff to provide the intervention. Four studies (n=7142) reported the effects of the intervention on smoking cessation. Of these, two studies found that the quit rate was higher in the intervention group than in the control group at 6 and 12 months' followup whereas the other two showed no difference between groups. There was some evidence for the effectiveness of the interventions on secondary outcomes such as documentation of smoking status and provision of cessation counseling, but each outcome was not consistently reported and several showed mixed effects (**Table 5**).[130]

Reduce-to-Quit Interventions

Most standard smoking cessation interventions, including most of the interventions synthesized above, encourage quitting smoking abruptly on a designated quit day. One recent high-credibility review by Lindson (2019c) assessed the effect of reduction-to-quit interventions versus no cessation intervention or abrupt quitting on long-term (6 months or more) cessation.[105] Trials that included at least one arm where smokers were advised to reduce their smoking consumption before quitting smoking altogether were included. This advice could be delivered through self-help materials or behavioral support or alongside smoking cessation medications. Fifty-one trials (n=22,509) were identified. Compared with no smoking cessation intervention, there was no evidence that reducing smoking consumption before quitting was more effective for abstinence at 6 months or greater (RR 1.74 [95% CI, 0.90 to 3.38]; I^2=45%; k=6; n=1599) and no evidence that reducing consumption was superior (or inferior) to abrupt quitting (RR 1.01 [95% CI, 0.87 to 1.17]; I^2=29%; k=22; n=9219) (**Table 5**).[105]

Interventions for Relapse Prevention

A separate moderate-credibility review by Livingstone-Banks (2019a) focused on relapse prevention interventions for tobacco cessation.[108] While there is no clear definition of a relapse prevention intervention, in general, relapse prevention is considered to apply to interventions that explicitly seek to reduce relapse rates after an acute treatment phase is successfully completed, or at some time after the quit date. The duration of the acute treatment phase varies, leading to variability in the post at which measurement of a relapse prevention effect begins. Studies of interventions for relapse prevention may randomly assign people who have already quit, or they may randomly assign smokers before their quit attempt and provide a general smoking cessation intervention to all participants, in addition to an extra component provided for those randomly assigned to relapse prevention.[108]

The 77 studies included in the review were highly variable and included both pharmacologic and behavioral interventions to help prevent relapse.[108] They (a) focused on people who had already quit or (b) helped people to quit, then tested treatments to prevent relapse. Several studies centered on special populations that needed to stop smoking for a limited period of time because they were pregnant (18 studies), in a hospital (5 studies, or serving in the military (3 studies). Analyses of behavioral interventions among abstainers did not detect an effect in both studies of assisted abstainers (RR 0.99 [95% CI, 0.87 to 1.13]; I^2=56%; k=10; n=5408) and unaided abstainers (RR 1.06 [95% CI, 0.96 to 1.16]; I^2=1%; k=5; n=3561) from the general population. Twelve included studies focused on pharmacologic interventions for existing abstainers (either unaided or following cessation pharmacotherapy, 11 studies) or for those that were randomly assigned extended treatment (1 study). There was some evidence that extending varenicline could be beneficial in preventing relapse, but it was only reported by two studies. NRT was found to help in unassisted abstainers, but no difference was seen among those who achieved abstinence with NRT. None of the six studies that examined the use of bupropion to prevent relapse found a statistically significant effect.[108]

Ancillary and Population Subgroup Effects

Two reviews specifically explored the differences in the effectiveness of pharmacotherapy according to sex[112, 124] and were discussed within the sections on pharmacotherapy results. Nineteen additional reviews synthesized the evidence on the benefits of pharmacotherapy or behavioral interventions among specific subpopulations of adults (**Table 2**). These included: eight reviews limited to persons with severe mental illness;[80, 100, 101, 118, 120, 133, 136, 142] two limited to those with or in treatment for alcohol or drug dependence;[81, 132] five focused on adapted interventions for ethnic minorities[86, 99, 107] or otherwise disadvantaged persons;[83, 139] two limited to smokeless tobacco users;[92, 123] one among individuals categorized as not motivated to quit,[141] and one that explored the effectiveness of pharmacotherapy by subgroups defined by genetically informed biomarkers.[122] Within these 19 reviews, most included trials were *limited* to these subpopulations and very few included trials (or reviews) addressed the relative effectiveness according to subgroup (e.g., the relative effects among those with or without depression). Results of these reviews were consistent with the broader evidence among general adult populations (reviews in which many of these subpopulation studies were included) and suggested effectiveness of both pharmacotherapy and behavioral interventions, alone and combined, to quit

smoking. Where pooled results were presented, the direction and magnitude of effects was almost identical to that seen with the broader evidence base, although the number of studies within each review was considerably smaller given the focus on specific subpopulations.

E-Cigarettes

We identified five fair-quality RCTs (reported in 10 publications) that evaluated the effectiveness of using e-cigarettes to help current conventional smokers stop or reduce smoking compared with placebo or nicotine replacement therapy (**Table 6**).[143-145, 151-157] The five trials all took place outside of the United States with one in the United Kingdom, one in Italy, one in Korea, and two in New Zealand. The mean age of enrolled smokers was 41 to 44 years in all five trials. Three trials enrolled mostly females (~60-70%) whereas one enrolled only males, and the other enrolled mostly males (36.7% female). Smokers within all five trials were heavy smokers with the median cigarettes smoked per day ranging from 15 to 20 and most had tried to quit in the past year. Further demographic details of the enrolled samples were sparsely reported (**Appendix F Table 1**). The types of e-cigarettes, nicotine content, delivery of the intervention, and additional intervention components differed across all five trials as did the comparisons (**Appendix F Table 2**). One trial compared 1) NRT patch plus a nicotine e-cig (18 mg/mL), 2) NRT patch plus a nicotine-free e-cig (0 mg/mL), and 3) NRT patch only. Another trial compared 1) nicotine e-cig (18 mg/mL) to 2) any form of NRT. Another trial compared 1) nicotine e-cig (16 mg/mL), 2) nicotine patch (21 mg), and 3) nicotine-free e-cig. A small Korean trial in males compared nicotine e-cigarettes (0.01 mg/mL) with nicotine gum (2mg/tablet). And, the final trial compared 1) nicotine e-cig (7.2 mg/mL) for 12 weeks, 2) nicotine e-cig (7.2 mg/mL for 6 weeks followed by 5.4 mg for 6 weeks), or 3) nicotine-free e-cigs. Whereas one trial allowed participants to use any brand of e-cigarette with any concentration of nicotine after a 4-week run-in period with a starter kit, four trials provided participants with e-cigarette cartridges for the whole study period. Of the five e-cigarettes evaluated for cessation, only the eVOD device (Walker trial), OneKit Aspire (TEC trial), and eGo-C (Lee trial) are currently available in US markets; the Elusion e-cigarette model used in the ASCEND trial has been discontinued and the Categoria e-cigarette (ECLAT trial) is not sold in US markets.

The largest trial, conducted in New Zealand, randomized participants to a 12-week treatment phase of 1) a nicotine patch plus a nicotine e-cig (n=500); 2) a nicotine patch plus a nicotine-free e-cig (n=499), or 3) a nicotine patch only (n=125).[155] All three groups also received behavioral counseling, although compliance data indicated that the patch plus nicotine e-cig group received more calls than the patch-only group. After 6 months following the agreed-upon quit date, verified continuous abstinence was statistically significantly higher in the patches plus nicotine e-cig group (7%) versus the patch plus nicotine-free e-cig group (4%) (RR 1.75 [95% CI, 1.02 to 2.98; p=0.038) but not the patch-only group (2%) (RR 2.92 [95% CI, 0.91 to 9.33]; p=0.05) (**Table 7**). Complete case and per-protocol analyses produced similar results with differences found between the two e-cig groups but not the nicotine-containing e-cig versus patch only groups. Absolute rates of self-reported quitting at 6 months were considerably higher than verified abstinence in all three groups (patch plus nicotine e-cigs: 18%, patch plus nicotine-free e-cigs: 11%, and patches only: 8%) with statistically significant differences found when comparing the nicotine-containing e-cigs to the other two groups, respectively.[155]

Median time to relapse (defined as smoking at least 5 cigarettes in the past 7 days) did not differ significantly between the patch plus nicotine e-cig group (193 days) versus the patch plus nicotine-free e-cig group (153 days) (hazards ratio [HR] 0.85 [95% CI, 0.70 to 1.03]; p=0.01) or patch only group (160 day (HR 0.90 [95% CI, 0.63 to 1.28; p=0.56).[155] Thirty-nine percent of the participants in the patch plus nicotine e-cig group relapsed within 6 months versus 43 percent of participants in the patch plus nicotine-free e-cig group and 31 percent of participants in the patch only group. Furthermore, in those still smoking at 6 months, there was no significant difference in change from baseline in the average number of cigarettes smoked per day or the proportion who reduced the number of cigarettes smoked per day by at least 50 percent.[155]

The results of this trial should be interpreted in light of some considerable limitations including high and differential loss to followup: at 6 months, only 50 percent of participants in the patch-only group were retained as opposed to 68 percent in both the nicotine and nicotine-free e-cig groups.[155] The majority of participants in the patch group who withdrew did so immediately post-randomization citing not wanting to be in that group. Furthermore, of those retained in the patch-only group, 15 percent crossed over and used an e-cigarette during the trial, with most crossing over within the first 6 weeks. Similarly, 11 percent of those randomized to the nicotine-free e-cig group crossed over to using nicotine-containing e-cigarettes. Detection bias was also likely with 70 percent of the nicotine e-cig group correctly identifying the presence of nicotine in their e-liquid. At 6 months, 22 to 40 percent of participants in all three groups were still using the patch whereas 49 to 56 percent of participants were still using an e-cig only or both a patch and e-cig.[155]

In another large trial (the TEC trial) in the United Kingdom, Hajek and colleagues randomized 886 smokers participating in National Health Services stop-smoking services to tobacco flavored e-cigarettes with 18 mg nicotine/ml (intervention group) or any form of NRT (comparison group).[154, 156] Both groups received 4 weeks of behavioral counseling. The primary outcome was abstinence at 1 year, defined as self-report of not more than five cigarettes from the target quit date, validated by expired CO<8 parts per million (ppm). At 1 year, 18 percent in the e-cigarette group were abstinent from smoking, compared with 9.9 percent in the comparison group (RR 1.83 [95 % CI, 1.30 to 2.58]) (**Table 7**). However, 80 percent of abstinent subjects assigned to the intervention group were still using e-cigarettes, compared with 9 percent in the comparison group continuing to use nicotine replacement therapy at 1 year. Overall loss to followup was 21 percent (19% in the e-cigarette group and 23% in the NRT group).[154]

In the ASCEND trial, Bullen and colleagues randomized 657 smokers in New Zealand who wanted to stop smoking to one of three interventions: 16 mg nicotine e-cigarette (n=285), 21 mg nicotine patch (n=295), or placebo e-cigarette (n=73).[144] 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 that called them directly; participants who declined or did not call back were still able to access other quitline support such as text messages. The primary outcome, abstinence at 6 months, was verified by exhaled CO<10ppm. Tobacco smoking cessation was generally low in all three groups: 7.3 percent with e-cigarettes, 5.8 percent with nicotine patches (RR for nicotine e-cigarettes vs. patches 1.26 [95% CI, 0.68 to

2.34]), and 4.1 percent with placebo e-cigarettes (RR for nicotine e-cigarettes vs. placebo 1.77 [95% CI, 0.54 to 5.77]) (**Table 7**). Thirty-eight percent of those who were abstinent and assigned to e-cigarettes still used e-cigarettes at 6 months, although it was unknown whether they were using nicotine or non-nicotine cartridges. There was differential loss-to-followup between groups at 6 months: 27 percent of those assigned to the patch versus 17 percent and 22 percent of those randomized to the nicotine and placebo e-cigarette groups, respectively.[144]

In a secondary analysis of cessation data from the ASCEND trial, O'Brien and colleagues examined the effectiveness of e-cigarettes among patients with (n=86) and without (n=571) a mental illness (defined as taking prescription medication for a diagnosed mental illness) at the time of randomization.[151] At the 6-month followup among participants randomized to e-cigarettes, there were no significant differences in smoking cessation between people with (5%, n=2/39) and without mental illness (n=7%, 19/250) (p=0.75). Among those with a mental illness (n=86), there were no significant differences in quit rates among those randomized to e-cigarettes (5%, 2/39) had biochemically verified smoking abstinence) as compared with those who used nicotine patches (14%, 5/35) (p=0.245). Among participants with mental illness randomized to placebo e-cigarettes, none had achieved cessation at 6 months (**Table 7**).[151]

Caponnetto and colleagues conducted an RCT in Italy, the ECLAT trial, in which 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.[145] The appearance of the cartridges was 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 1 year, abstinence rates (verified by <7.5 ppm exhaled CO) were 11 percent for participants in the combined nicotine groups compared with 4 percent in the group receiving no-nicotine cartridges (p=0.04) (**Table 7**). At the 1-year assessment, 26.9 percent of all study participants were still using e-cigarettes. There was substantial loss to followup in the study: no followup data was available for 36 percent of those randomized to one of the nicotine-containing cartridges and 45 percent of those receiving no-nicotine cartridges.[145]

Lee and colleagues conducted a small RCT in male workers from a Korean motor company, randomizing 150 participants to receive a 12 week supply of either e-cigarettes or nicotine gum.[157] Eligible participants smoked at least 10 cigarettes per day for the past year, had smoked for at least three years, and were motivated to stop or reduce their cigarette smoking. All participants received a fifty-minute education session on smoking cessation and use of smoking-cessation aids and they were instructed to visit the medical office every four weeks for evaluation and counseling from an independent health practitioner. Continued abstinence was verified using self-report questionnaires and both end-expiratory carbon monoxide (<10 ppm) and urine cotinine (negative result). Biochemically validated continued abstinence rates from weeks 9 to 24 did not differ significantly between the groups (21.3% vs. 28% (p=0.344) in the e-cigarette group and nicotine group respectively) (**Table 7**). The seven-day point prevalence abstinence at 24-weeks was similar, with 22.7 percent in the e-cigarette group and 29.3 percent in the nicotine gum group reporting no smoking (p=0.352).[157]

Key Question 3. What Harms Are Associated With Tobacco Cessation Interventions in Adults?

Combined Pharmacotherapy and Behavioral Interventions

None of the included reviews synthesized the evidence on harms related to combined pharmacotherapy and behavioral support versus no or minimal interventions. Any harms of combined therapy are assumed to be like those of the pharmacotherapy being used.

Pharmacotherapy Interventions

We included nine primary reviews[85, 87, 96, 98, 104, 113, 114, 128, 131] that reported AEs related to pharmacotherapy interventions for smoking cessation in general adult populations. In addition, six reviews[80, 101, 118, 120, 133, 142] addressed the harms of pharmacotherapy among persons with severe mental illness.

Nicotine Replacement Therapy

Harms related to NRT use were reported in four reviews among the general adult population[96, 104, 113, 114] and one review among persons with severe mental illness.[120] All five of these reviews were rated as moderate or high credibility. AEs from the use of NRT are typically related to the type of product and include skin irritation from patches and irritation to the inside of the mouth from gum and lozenges.[96, 104, 114] Pooled results from multiple reviews indicate a higher risk of heart palpitations and chest pains, or any CV event (any clinical diagnoses of a CV event including minor events such as palpitations, bradycardia, and arrhythmia) from NRT versus non-NRT control groups (**Table 8**).[96, 113, 114] For instance, among non-high-risk adults, one review found an approximate 80 percent increase 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).[113] A sensitivity analysis found that these treatment effects were driven predominantly by more minor CV events, however, including bradycardia and arrhythmia, and occurred primarily in studies with longer followup periods. When restricted to major adverse CV events (defined by the FDA as a combined outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), pooled results did not clearly establish harm (RR 1.38 [95% CI, 0.58 to 3.26]; I^2=0%), but the confidence interval was quite wide and incorporated potential benefit as well as significant harm and the overall number of SAEs was very low.[113] Pooled results also found an increased risk of NRT versus non-NRT control for nausea and vomiting (although patch users had a decreased risk), gastrointestinal complaints, and insomnia.[114] There was no statistically significant increased risk of headache, dizziness, anxiety or depression, or mortality.[114] 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%; k=8; n=2765).[96]

There was no evidence of an effect on cardiac AEs, SAEs, or withdrawals when looking at different forms, deliveries, doses, durations, and schedules of NRT (**Table 8**).[104] Furthermore, there was no evidence of a difference in harms, including a worsening of psychiatric symptoms,

related to NRT within three reviews that focused on trials limited to smokers with severe mental illness.[120]

Bupropion

Harms related to bupropion use were reported in two moderate-to-high credibility reviews among unselected adults[98, 113] and one moderate credibility review among persons with severe mental illness.[120] The Howes review (2020) examined SAEs reported in 21 trials of bupropion versus placebo or no pharmacotherapy control, including trials that were excluded from their efficacy analysis because of short followup (i.e., less than 6 months).[98] SAEs 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. Meta-analysis of 21 trials did not provide clear evidence that the use of bupropion increased the risk of SAEs control (RR 1.16 [95% CI, 0.90 to 1.48], I^2=0%; k=21; n=10,625), with very low SAE rates of 2.3 percent for bupropion users and 2.4 percent for placebo users or non-bupropion participants (**Table 8**).[98]

A separate older review (Mills 2014) suggested no significant increased risk of any CV event for bupropion versus placebo (RR 1.03 [95% CI, 0.71 to 1.50], I^2=0%; k=27; n=10,402) (**Table 8**).[113] 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 8**). 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. In the recent EAGLES trial, there was no significant difference in the incidence of cardiovascular events during treatment between those on bupropion versus placebo, nor a significant difference in time to onset of major cardiovascular AEs (hazard ratio [HR] 0.50 [95% CI, 0.10 to 2.50]).[164]

In the review by Howes there was evidence to suggest that participants randomized to bupropion were more likely to report psychiatric AEs compared with those randomized to placebo.[98] A pooled analysis of six placebo-controlled trials found a 25 percent increased risk of any neuropsychiatric AEs among those taking bupropion (RR 1.25 [1.15 to 1.36]; k=6; n=4439).[98] In the Howes review, all neuropsychiatric events and symptoms were included regardless of severity.[98] Conversely, when limited to moderate or severe neuropsychiatric events, the EAGLES trial found was no evidence of a significant increase in neuropsychiatric AEs attributable to bupropion relative to nicotine patch or placebo.[161, 165] The primary endpoint in this trial was a composite measure based on post marketing reports of neuropsychiatric AEs in smokers taking bupropion and varenicline and included 16 neuropsychiatric symptom categories. The overall incidence of neuropsychiatric AEs was similar across the bupropion (4.5%, 90 of 2006 participants), nicotine patch (3.9%, 78 of 2022 participants), and placebo (3.7%, 74 of 2014 participants) groups. For both the nonpsychiatric and psychiatric cohort, there was no significant difference in neuropsychiatric AEs in those assigned to bupropion versus placebo (risk difference [RD] -0.08 [95% CI, -1.37 to 1.21], n=1988 and RD 1.78 [95% CI, -0.24 to 3.81], n=2032), respectively. Likewise, there was no difference between the bupropion and placebo groups in rates of suicidal behavior and ideation.[161, 165]

A separate moderate-credibility review by Roberts (2016) synthesized the direct and indirect evidence on pharmacologic tobacco cessation treatment among adult smokers with any form of severe mental illness, defined as any nonorganic disorder with psychotic features that results in a substantial disability including schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder or depressive psychoses.[120] Harms were measured using a tolerability outcome which equaled the number of patients discontinuing the trial due to any adverse event. Across six trials that compared bupropion with placebo, three trials reported that no participants in either group discontinued the trials because of AEs. In the remaining three trials, two found greater rates of dropout among those in the placebo group versus bupropion group, whereas the remaining found five versus two dropouts due to AEs among the bupropion versus placebo groups, respectively. Pooling all six trials showed no statistically significant difference between groups (OR, 0.93 [95% CI, 0.18 to 4.74]; I^2=26%; k=3; n=201) (**Table 8**).[120]

Varenicline

Harms related to varenicline use were reported in three reviews among unselected smokers, [85, 128, 131] four reviews among persons with severe mental illness,[80, 101, 120, 142] and one review limited to smokeless tobacco users.[123] The most commonly reported adverse effect of varenicline was nausea, which was mostly at mild to moderate levels and usually subsided over time. Other common side effects of varenicline versus placebo with a statistically significant increase were insomnia, abnormal dreams, headache, and fatigue.[85, 131] A meta-analysis of SAEs occurring during or after active treatment suggested there may be a 25 percent increase in the chance of SAEs among people using varenicline compared with placebo (RR 1.25 [95% CI, 1.04 to 1.49]; k=29; 15,370) (**Table 8**); however, many of these events included comorbidities that were mostly considered by the trialists to be unrelated to the treatments. Across all reviews, very few deaths were reported in the included trials and no review found a difference in all-cause mortality between varenicline and placebo.[128, 131]

Pooled analyses representing over 12,000 participants do not indicate a statistically significant increased risk of cardiovascular events (**Table 8**).[85, 113, 128] For instance, within the Mills (2014) review, among 18 trials comparing varenicline with placebo, there was no evidence of an increased risk of cardiovascular AEs (RR 1.24 [95% CI, 0.85 to 1.81]; I2=0%; k=18; n=9072) of major cardiovascular AEs among adults (RR 1.44 [95% CI, 0.73 to 2.83]; I2=0%; k=18; n=9072).[113] Similarly, in a more recent low-credibility review, when pooling data across 38 studies, the review by Sterling (2016) found no significant difference for cardiovascular SAEs when comparing varenicline (57 events within 7213 participants) with placebo (43 events within 5493 participants) (RR 1.03 [95% CI, 0.72 to 1.49]).[128] Furthermore, similar results were found among patients with and without a history of cardiovascular disease.[128]

There was also no evidence of a statistically significantly higher risk of neuropsychiatric AEs for those on varenicline versus placebo (**Table 8**).[85, 131] In the most recent review by Cahill (2016), 23 trials representing nearly 9000 smokers found no difference in the number of people experiencing a neuropsychiatric event between those randomized to varenicline versus placebo (RR 0.82 [95% CI, 0.57 to 1.19]).[85] Likewise, in the review by Thomas (2015), there was no evidence of an increased risk of suicide or attempted suicide (Peto OR 1.67 [95% CI 0.33 to 8.57]), suicidal ideation (Peto OR 0.58 [95% CI, 0.28 to 1.20]), or depression (Peto OR 0.96

[95% CI, 0.75 to 1.22]) associated with varenicline.[131] There was no evidence that the risk of depression and suicidal ideation differed by age, sex, ethnicity, smoking status, the presence or absence of psychiatric illness, or study sponsorship. The effect estimates (Peto OR) for the trials in which all participants had psychiatric illnesses compared with those where none of the participants had psychiatric illness were 0.79 (95% CI, 0.32 to 1.93) versus 0.34 (95% CI, 0.09 to 1.29) for suicidal ideation and 1.49 (95% CI, 0.84 to 2.65) versus 0.91 (95% CI, 0.69 to 1.21) for depression.[131] Four other reviews similarly found no differences in neuropsychiatric AEs or discontinuation due to AEs between smokers with severe mental illness taking or not taking varenicline (**Table 8**).[80, 101, 120, 142] Finally, no differences in the rates of nausea, sleep disturbances, or mood disorders were seen within three trials testing the effectiveness of varenicline versus placebo among smokeless tobacco users.[123]

Other Medications

There was insufficient evidence to indicate whether other antidepressants such as nortriptyline, SSRIs, or MAOIs increased the risk of AEs relative to placebo given too few trials for each comparison.[98]

In general, four trials of cytisine that all reported on harms did not identify more AEs or SAEs in the intervention versus control arm, but this data is limited by the few numbers of trials and lack of reporting at longer followup.[85]

Behavioral Interventions

Only three of the reviews on behavioral interventions included any discussion of potential harms from behavioral-based tobacco cessation interventions, including the review on internet-based interventions,[129] the review on incentives,[116] and the review on hypnotherapy.[82] There was no clear harm related to any of these interventions. In the review on internet-based interventions, few trials reported AEs (6 of 67 included trials) and in those that did, AEs were rare and minor (i.e., weight gain, perceived stress, sleep disorder, fatigue).[129] In the review on incentives for smoking cessation, one trial found no evidence of worsened psychiatric symptoms among smokers with serious mental illness. None of the other included studies reported on any harms, unintended consequences or AEs associated with the offering incentives.[116, 166] The Barnes review looked for reported AEs among participants taking part in hypnotherapy interventions and found that none of the 14 included studies reported AEs.[82]

Reduction-to-Quit Interventions

The review by Lindson (2019c) reported no clear evidence that the number of people reporting SAEs, or changes in withdrawal symptoms, differed between those advised to reduce their smoking versus those receiving no advice or advice for abrupt quitting; although pre-quit AEs, SAEs, and withdrawal symptoms were measured and reported variably and infrequently across studies.[105]

E-Cigarettes

The five RCTs that evaluated the effectiveness of e-cigarettes to aid in efforts to quit smoking conventional cigarettes at 6 months or longer,[144, 145, 154, 155, 157] as well as four RCTs of e-cigarettes with shorter followup periods,[146-148, 150] were included in the evaluation of e-cigarettes' harms. No cohort studies met criteria for inclusion. Characteristics of studies included for harms are described in **Table 6** and **Appendix F Tables 1 and 2**.

None of the studies reported statistically significant differences in SAEs between intervention and control groups (**Table 9**).[144-148, 150, 154, 155, 157] Four of the five trials that evaluated e-cigarette effectiveness reported nonsignificant distributions of AEs between the intervention and control groups at ≥6 months of followup (**Table 9**).[144, 145, 154, 155] The ASCEND trial, conducted by Bullen and colleagues, found no statistically significant difference in the incidence rate ratio (IRR) for AEs between these groups at 6 months' followup (IRR 1.05 [95% CI, 0.82 to 1.34], p=0.7), despite a higher number and proportion of SAEs occurring in the nicotine e-cigarette group (27 serious events, 19.7%) than in the nicotine patch group (14 events, 11.8%).[144] The authors deemed none of the AEs to be related to product use in any of the treatment groups.[144] Similarly, the ECLAT study by Caponnetto and colleagues found no difference in the frequency of AEs among study groups at 12 and 52 weeks.[145] No serious events occurred during the study.[145] In the TEC trial, Hajek and colleagues reported that, as compared with participants assigned to NRT, those assigned to e-cigarettes had higher rates of throat and mouth irritation (e-cigarettes: 65.3% vs. NRT: 51.1%; RR 1.27 [95% CI, 1.13 to 1.43]) and lower rates of cough (e-cigarettes: 30.8% vs. NRT: 39.8%; RR 0.8 [95% CI, 0.6 to 0.9]) at 12 months of followup.[154] SAEs occurred in both groups, but the trial clinicians determined that none of these events were attributable to study product use (**Table 9**).[154] In a recent trial, SAEs occurred in 16 participants in the patch plus nicotine e-cig group, 22 people in the patch plus nicotine-free e-cig group, and 3 people in the patch only group; although the incidence rate ratios between group were not statistically significant and the authors deemed that none of the SAEs were considered treatment related.[155] Another recent trial reported no SAEs among participants in either group but reported that the percentage of participants who experienced any adverse event was significantly lower in the e-cigarette group than in the nicotine gum group (6.7% vs 17.3% in e-cigarette group and nicotine gum group respectively)[157] (**Table 9**).

Among the four trials newly identified by this review with followup periods <6 months, no significant differences in the incidence of AEs overall or SAEs between intervention and control groups were reported (**Table 9**).[146-148, 150] At four months of followup, Carpenter and colleagues found that participants in a U.S. trial who were randomized to e-cigarettes (either 16 mg/mL or 24 mg/mL nicotine concentration), as compared with participants with ongoing conventional cigarette (CC) use, reported higher rates of cough (e-cigarettes: 32% vs. CCs: 21%), but exhibited similar rates of throat irritation (e-cigarettes: 16% vs. CCs: 17%).[147] Although differences in the incidence of AEs between the intervention and control groups were observed, statistical comparisons were not made, and no AEs resulted in study withdrawal.[147] Similarly, Cravo and colleagues, comparing e-cigarettes with ongoing CC use in the United Kingdom at 4 months, found higher rates of cough (e-cigarettes: 17.0% vs. CCs: 7.8%), sore throat (e-cigarettes: 27.8% vs. CCs: 8.8%), and headache (e-cigarettes: 47.4% vs. CCs: 33.3%), but no statistical comparisons were made.[148] Compared with a nonnicotine-containing e-cigarette

(placebo), Masiero and colleagues found the subjects who used nicotine-containing e-cigarettes reported higher rates of burning throat (e-cigarette: 5.7% vs. placebo: 2.9%) and cough (e-cigarette: 10.0% vs. placebo: 2.9%) at 3 months of followup, but statistical comparisons were not made.[146] In a study by Tseng and colleagues, young adult smokers in the United States who were randomized to low-nicotine (4.5%) e-cigarettes reported almost twice the proportion of AEs (22.5%) over a 3-week followup period as participants randomized to no-nicotine placebo e-cigarettes (10.3%); however, this difference was not statistically significant (p=0.14).[150]

Evidence for Pregnant Women

Included Evidence

Based on a primary literature review of 64 full-text articles, we identified seven RCTs (reported in 12 publications)[167-178] evaluating the use of NRT among pregnant women and five large observational studies (reported in six publications)[179-184] that reported on the harms of NRT, bupropion, or varenicline use (**Appendix B Figure 3**).

Using the overview of reviews approach, we identified five reviews that addressed the benefits and harms of behavioral interventions for supporting women to stop smoking pregnancy (**Table 2**).[108, 116, 185-187] The review by Chamberlain (2017) included any behavioral support intervention including counseling, health education, feedback, incentives, social support, exercise, and dissemination of cessation interventions.[185] The included bodies of evidence within the three other reviews focused on digital interventions,[186] incentives,[116, 187] and psychotherapy[187] were mostly duplicative and the results were entirely consistent with those of Chamberlain. Additionally, one review on relapse prevention provided a detailed synthesis of interventions among pregnant women and is reported below.[108]

We identified no studies that met eligibility criteria that addressed the benefits or harms of the use of e-cigarettes to help pregnant women quit smoking.

Credibility/Quality Assessment

Of the seven RCTs included that examined the benefits and harms of NRT among pregnant women, we rated two as good quality and the remaining five as fair quality (**Table 10**). Increased risk of bias in the fair quality studies was primarily owing to lack of allocation concealment, attrition, and study arm imbalances in baseline characteristics. Of the five observational studies included for harms, we rated four of them as good quality and one as fair quality. The fair quality study was assessed to have elevated risk of bias due to limitations in the data source for assigning individuals to the exposed and unexposed groups and insufficient adjustment for possible confounding factors.

The review by Chamberlain (2017) was rated as having high credibility according to AMSTAR-2 criteria and had no critical weaknesses. The other reviews that included evidence for pregnant

women were all rated as moderate or high credibility with only minor weaknesses in the methodology noted.

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

Pharmacotherapy Interventions

Nicotine Replacement Therapy

All seven included RCTs were designed to test the effectiveness of NRT on smoking cessation and reported infant, child, and maternal health outcomes (**Table 10**).[167, 168, 171, 174-176, 178] Most evaluated NRT patch interventions, but one gave participants a choice of patch, gum, or lozenge,[176] one trial offered NRT gum,[174] and one used a nicotine inhaler[175] (**Appendix G Table 2**). In all cases, women were offered behavioral support in addition to NRT. Five of the seven RCTs were placebo controlled. The largest study (n=1050) was the Smoking, Nicotine, and Pregnancy trial (SNAP), which was a multisite RCT of NRT patches conducted in the United Kingdom.[168-170] The second largest and most recent NRT trial was conducted in France at multiple sites, randomizing 402 women to nicotine patches or placebo nicotine patches.[167] Women enrolled in the seven trials were mainly ages 18 years and older (mean ages ranged from 25.1 to 29.3 years).[167] One trial exclusively enrolled African-American women.[171] Study recruitment tended to be at the first antenatal visit or before the end of the second trimester of pregnancy; one small trial allowed women to enroll any time before 30 weeks gestation but the average gestation at baseline was in the early second trimester (**Appendix G Table 1**).[171] In one trial[174] women were invited to participate if they smoked one or more cigarettes per day during pregnancy and in the other trials five or more cigarettes per day. Five trials, including the two largest, reported the percentage of participants with a history of preterm birth (range 9% to 15%).[167, 168, 174-176] Low adherence to NRT therapy was noted in the trials. For example, in the SNAP trial;[168-170] only 7.2 percent of women in the NRT condition and 2.8 percent with placebo used the patch for more than one month, and in the trial offering a choice of gum, patch, or lozenge,[176] the average use of NRT was lower than the prescribed and dispensed medications.

Five placebo-controlled trials reported on preterm birth (delivery at <37 weeks gestation). [167, 168, 174, 175, 178] The most recent study reported a statistically significant lower incidence of preterm delivery among those in the NRT inhaler group (3/67, 4%) compared with the placebo group (10/67, 15%) (p=0.030 after controlling for history of preterm birth).[175] Within the other trials, one reported similar numbers of women with preterm birth in the NRT and placebo arms (14.0% vs. 13.5%, respectively),[167] two reported only slightly fewer women with preterm birth in the NRT arm,[168, 178] and the smallest study reported reduced incidence of preterm birth with NRT compared with placebo (RR 0.39 [95% CI, 0.17 to 0.91]) (**Appendix G Figure 1**).[174] The three placebo-controlled trials that did not report statistically significant differences had larger samples and estimated effects closer to null, ranging from a RR 0.85 to 1.04.[167, 168, 178] Two trials without placebo controls were imprecise and estimated effects in opposite directions.[171, 176]

All seven trials reported the association between the intervention and mean birthweight.[167, 168, 171, 174-176, 178] Two placebo-controlled trials found significantly higher birthweights among women allocated to the NRT arm[174, 178] (**Appendix G Figure 2**), while only one of the trials[174] reported similar effect for the proportion of infants categorized as having low birthweight (**Appendix G Figure 3**). The two largest, good-quality, placebo-controlled trials of NRT patch interventions, did not find evidence of increased infant birthweight with NRT treatment.[167, 168] Further, Coleman and colleagues found more low birthweight infants were reported for the NRT condition, although the result was not statistically different from null (RR 1.38 [95% CI, 0.90, 2.09).[168] Four trials also reported stillbirths, but low event rates and imprecision limit inference (**Appendix G Figure 4**).[167, 168, 174, 176]

The trial by Coleman and colleagues, reported 2-year followup data on child health outcomes.[168-170, 173] In this trial, just under one-third of participants in each arm completed the 2-year questionnaire. Nonrespondents' family physicians 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 (NRT n=445 and placebo n=446). Comparison group characteristics were similar in the original and followup cohort. 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, and sensory) and respiratory problems (i.e., respiratory symptoms, asthma diagnosis, and admissions to hospital for respiratory problem). Group comparisons using intention-to-treat analyses with multiple imputation indicated that survival with no impairment was significantly higher among those allocated to the NRT group compared to placebo (73% versus 65%; OR 1.40 [95% CI, 1.05 to 1.86]). There was no significant difference in rates of definite developmental impairment (11% NRT, 14% placebo; OR 0.71 [95% CI, 0.47 to 1.09]) between the groups. For respiratory problems, a 5 percent observed difference between the arms (30% NRT vs. 25% placebo) was not statistically significant (OR 1.30 [95% CI 0.97 to 1.74]).[169, 170] Results from a complete case analysis that included twins were consistent with these results.[169]

Bupropion

We identified no trials that addressed the effectiveness of bupropion among pregnant women that met our eligibility criteria.

Varenicline

We identified no trials that addressed the effectiveness of varenicline among pregnant women that met our eligibility criteria.

Behavioral Interventions

The review by Chamberlain (2017) identified 102 trials that addressed the effects of smoking cessation interventions during pregnancy on smoking behavior and perinatal health outcomes (**Tables 2** and **3**).[185] Most of the trials in this review included generally healthy women over 16 years of age, while two trials targeted women younger than 20 years of age, eight trials

specifically targeted women with psychosocial risk factors, and two trials were limited to women under methadone treatment for opioid addiction (**Table 4**). About half the trials (k=52, 66 study arms) explicitly recruited women categorized as having low socioeconomic status, and 10 trials included mainly women belonging to an ethnic minority population. Most of the included trials recruited women during their first antenatal visit or second trimester of pregnancy and excluded women in their last trimester of pregnancy due to the limited time available to receive an intervention. There were, however, four trials that targeted women who smoked into late pregnancy.[185]

Within the trials that were included for any meta-analysis, 94 were aimed exclusively at supporting smoking cessation and 12 trials aimed to improve maternal health, which included smoking cessation.[185] The latter studies were only included for KQ 2 (cessation outcomes) given that there is a potential for other aspects of these interventions to have impacted birth outcomes. All interventions differed substantially in their intensity, duration, and interventionists. Included trials presented many comparisons. Interventions included counseling, health education, feedback, incentives, social support, exercise, and dissemination (active dissemination of a smoking cessation intervention) and comparators included usual care, less intensive interventions, and alternative interventions (e.g., cognitive behavioral counseling versus traditional health education). The review excluded trials comparing efficacy of pharmacotherapy with equal levels of behavioral support. Of interventions categorized as counselling interventions (54 intervention arms), most involved face-to-face contact, using a variety of strategies either alone or in combination (such as motivational interviewing, cognitive behavioral therapy, stages of change). The duration and frequency of counseling varied considerably but has generally increased over time. Health education (12 intervention arms) were those interventions that provided information about the risk of smoking and advice to quit but did not give further support or advice on how to make this change. Most were provided through automated support such as self-help materials or automated text messaging. Feedback interventions (6 intervention arms) were those where the mother was provided feedback with information about the fetal health status or measurement of by-products of tobacco smoking to the mother. Incentive-based interventions (13 arms) included interventions were women received a financial incentive, contingent on their smoking cessation, including gift vouchers. Social support interventions (7 arms) were those that explicitly included the provision of support from a peer or partners.[185]

Of the 102 included trials, 26 study arms reported mean birthweight, 17 arms reported rates of low-birthweight babies (less than 2500 g) and three reported rates of very low birthweight babies (less than 1500 g), and 19 study arms reported rates of preterm births (less than 37 weeks' gestation).[185] Other, less commonly reported data included stillbirths (k=8), perinatal deaths (k=4), and neonatal deaths (k=5).[185]

When all 26 studies that reported mean birthweight were combined, there was evidence that infants born to women receiving behavioral smoking cessation interventions had an increase in mean birthweight of 55.60 g, compared with women in the usual care control groups (MD 55.60 g [95% CI, 29.82 to 81.38]; I^2=31%; k=26; n=11,338) (**Table 11**).[185] The magnitude and significance of the effect was similar when limited to counseling interventions (42.17 g [95% CI, 11.79 to 72.55], I^2=0%; k=14; n=5471), and a test for subgroup differences showed no evidence of effect modification by type of intervention (p=0.11). The magnitude of the mean difference

between groups for all types of interventions was modest, yet there was general consistency in the direction of effects across studies, with only six reporting effects (none statistically significant) favoring the control condition. Evidence of beneficial effects was also observed in the pooled analyses across all interventions and comparators for low birthweight (under 2500 g). The pooled effect estimate suggested a 17 percent risk reduction for delivery of a low birthweight baby (RR 0.83 [95% CI, 072 to 0.94]; I^2=0%; k=18; n=9402) (**Table 11**). When restricted to specific types of interventions, while results suggested similar benefits, none of the pooled results were statistically significant. None of the three trials reporting on rates of birth to very low birthweight babies (less than 1500 g) found a beneficial effect of the behavioral intervention versus control.[185]

Of the 19 trials reporting the effects of the intervention on preterm birth (less than 37 weeks), results were mixed, although the majority reported a reduced risk of preterm birth among women within the behavioral interventions versus control groups.[185] Meta-analysis of these trials resulted in uncertainty in the potential benefit of behavioral interventions compared with controls on rates of preterm birth (RR 0.93 [95% CI 0.77 to 1.11]; I^2=18%; k=19; n=9222) (**Table 11**). In separate comparisons of studies, the effect was also unclear across comparisons by type of specific intervention and control groups.[185]

Among the eight trials reporting stillbirth, none of the trials found significant differences between study groups, and the pooled result was consistent with either potential benefit or harm (RR 1.20 [95% CI, 0.76 to 1.90]; I^2=0%; k=8; n=6170) (**Table 11**).[185] There were very low event rates within each group across trials, however, overall, there were slightly more stillbirths recorded in the intervention groups (40/3053) compared with the control groups (33/3117). Three trials of counseling, one trial of a feedback intervention, and one exercise trial reported on neonatal deaths, but events were too rare to inform valid conclusions. Similarly, there was no pattern of effects across four trials reporting perinatal death.[185]

E-Cigarettes

We identified no trials that addressed the effectiveness of e-cigarettes among pregnant women that met our eligibility criteria.

Key Question 2. Do Tobacco Cessation Interventions Increase Tobacco Abstinence in Adults Who Currently Use Tobacco, Including Pregnant Women?

Pharmacotherapy Interventions

Nicotine Replacement Therapy

There was no evidence of differences in smoking cessation with NRT intervention across the included RCTs. Meta-analysis of five placebo-controlled trials generated a pooled effect of NRT on validated smoking cessation at followup (RR 1.11 [95% CI, 0.79 to 1.56]; I^2 = 0%, n=2033)

and low statistical heterogeneity (**Appendix G Figure 5**).[167, 168, 174, 175, 178] Quit rates in these trials ranged from 5 to 28 percent in the intervention groups and 5 to 25 percent in the control groups (mean,11.8% vs. 10.6%). The results across trials for the efficacy of NRT were relatively consistent, with effect estimates ranging from 1.08 to 1.24 in the placebo-controlled trials (with the exception of one new trial that found a higher quit rate among those in the placebo group [17.9%] compared with the NRT group [10%] (RR 0.56 [95% CI, 0.23 to 1.33]).[175] The results of the two smaller trials with no treatment controls[171, 176] were not statistically significant, and estimates of efficacy were greater than for the placebo-controlled trials. Including these studies in meta-analysis did not change the overall findings (data not shown). Low rates of adherence to the intervention were described (mean adherence rates of less than 25 percent were often observed); particularly in the trials with good reporting.[167, 168, 174, 175, 178]

The 2-year SNAP followup study found continuous smoking abstinence rates to be very low in both groups: 3 percent of mothers in the NRT group and 2 percent of mothers in the placebo group self-reported prolonged (or continuous) abstinence at two years since the quit date set in pregnancy, with no statistical difference between groups.[170] 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 no significant differences between groups earlier in the postpartum period (6 months), a significant effect was observed at one year (4% NRT vs. 2% placebo) with further adjustment (site, baseline salivary cotinine, partner smoking status, and years completed education).[170]

Bupropion

We identified no trials that addressed the effectiveness of bupropion among pregnant women that met our eligibility criteria.

Varenicline

We identified no trials that addressed the effectiveness of varenicline among pregnant women that met our eligibility criteria.

Behavioral Interventions

Primary Results

The review by Chamberlain (2017) identified 102 trials with 120 study arms testing the effects of a behavioral interventions for smoking cessation among pregnant women.[185] Of the 120 study arms included in the review, 97 arms reported the primary outcome measure of smoking abstinence in late pregnancy, up to and including the period of hospitalization for birth. In 71 of these study arms (73%), this abstinence was biochemically validated. In most trials, women were classified as “current smokers”; some other studies included women who had spontaneously quit in early pregnancy but are included here. The remaining trials did not report a measure of smoking abstinence in late pregnancy but focused on abstinence in the postpartum period only, smoking reduction, or perinatal outcome measures.[185]

Pooled analyses of all behavioral interventions (k=97), regardless of type and including self-reported outcomes, indicated a statistically significant effect on smoking cessation in late pregnancy when compared with usual care or a minimal intervention (RR 1.35 [95% CI, 1.23 to 1.48]; k=97; n=26,637), with moderate heterogeneity of estimated effects (I^2=44%) (**Table 12**).[185] While an overall Chi^2 test for subgroup differences found no difference by the type of intervention (p=0.39), the number of studies varied considerably by intervention type (counseling [51 trials], health education [11 trials], feedback [6 trials], incentives [13 trials], social support [14 trials], exercise [1 trial], and other [1 trial]. The results were similarly beneficial when restricted to trials comparing counseling with any type of control (RR 1.31 [95% CI, 1.16 to 1.47]; I^2=40%; k=51; n=18,2786) as well as when comparing counseling with usual care (RR 1.44 [95% CI 1.19 to 1.73]; I^2=49%; k=30; n=12,432). Results of trials of feedback and incentives were also suggestive of a benefit; but 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]). The effects of other types of interventions versus any comparator or usual care generally favored the intervention conditions, but pooled results did not rule out the possibility of no benefit. Direct comparisons between interventions of greater versus less intensity were found to be statistically significant for trials testing counseling, but not for the fewer studies of health education (4 trials), feedback (3 trials), or social support (7 trials) interventions (**Table 12**). There was some evidence that the positive effects of behavioral interventions on smoking cessation in late pregnancy continued into the postpartum period, up until approximately 18 months postpartum. For instance, in an examination of counseling interventions compared with usual care, the average RR was 1.59 (95% CI, 1.26 to 2.01; k=11) at 0 to 5 months postpartum, 1.33 (95% CI, 1.00 to 1.77; k=6) at 6 to 11 months postpartum, and 2.20 (95% CI, 1.23 to 3.96; k=2) at 12 to 17 months.[185]

Evidence of Effect Modification

Regarding the whole set of trials, meta regression analyses found no differences in the effects of behavioral interventions according to the specific intervention strategies, comparator, intensity (categorized according to frequency of contact), intervention duration, the provision of self-help manuals, including telephone support, the SES of the sample, newly added studies, or study design (cluster versus individually randomized trials).[185] In general, interventions of higher intensity typically also had control groups of higher intensity, potentially explaining why no clear differences were seen with increasing intervention intensity. There was some evidence that studies with a high risk of bias related to allocation concealment had a larger pooled-effect size estimate compared with lower risk or unclear risk of bias studies. Studies with unclear and low risk of bias for equal baseline characteristics in study arms showed larger effect sizes than those at high risk of bias for this item. No other measures of risk of bias (random sequence generation, attrition bias, selective reporting bias, detection bias, blinding, contamination, or intervention fidelity) predicted larger effect estimates.[185]

Several of the individual trials provided findings of subgroup analyses based on participant characteristics.[185] Of 13 studies that reported a sensitivity analysis by a measure of socioeconomic status with studies (such as education levels and employment), eight reported lower abstinence rates among women with lower SES, three reported no difference, and two reported higher rates of intervention success among women with low SES. Among the eleven

trials that reported outcomes by ethnic status results were inconsistent: one study reported the intervention was less effective among Hispanic and African American women compared with white women, one study reported the intervention was less effective among Hispanic compared with African American women, four studies reported no difference in outcomes by race or ethnicity, and five study arms reported higher quit rates among African American and/or Hispanic women compared with women of other races and ethnicities. Four studies reported a negative association between treatment effectiveness and higher rates of depression, and of six studies that reported measures of social support, four reported a negative association with low social support and quitting.[185]

Interventions for Relapse Prevention

The moderate-credibility review by Livingstone-Banks (2019a) included 18 trials focused on relapse prevention among pregnant and/or postpartum ex-smokers.[108] Pooled results from eight studies of interventions in pregnancy did not demonstrate a clear benefit on relapse prevention at the end of pregnancy (RR 1.05 [95% CI, 0.99 to 1.11]; k=8; n=1523; I^2=0%). There was also no significant benefit seen among 15 studies that included followup into the postpartum period overall or when subgrouped according to timing of the intervention (overall RR 1.02 [95% CI, 0.94 to 1.09]; k=15; n=4606; I^2=3%).[108]

E-Cigarettes

We identified no trials that addressed the use of e-cigarettes to quit smoking among pregnant women that met our eligibility criteria.

Key Question 3. What Harms Are Associated With Tobacco Cessation Interventions in Adults, Including Pregnant Women?

Pharmacotherapy Interventions

Nicotine Replacement Therapy – Trial Evidence

Given the low number of trials and high statistical heterogeneity, we did not report pooled analyses for health outcomes that could also be evaluated as potential harms of NRT treatment (e.g., stillbirth). The available trials (**Table 10**) were underpowered for assessing rare harms with statistical confidence.[167, 168, 171, 174-176, 178] As reported above, significant effects of NRT on health outcomes included beneficial effects for some individual studies, including higher birthweight in two trials[174, 178] and reduced risk of preterm birth in one.[174] Three trials reported miscarriage by study arm, but there were too few events in the study arms to draw valid inference and no difference was evident.[167, 168, 175]

The two large, good-quality NRT patch trials reported detailed maternal adverse events.[167, 168] In the Berlin trial, there was insufficient statistical 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%).[167] The trial did, however, report a statistically 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=0.01). Reported cases of preeclampsia were few, but consistent with the differences in blood pressure, preeclampsia was diagnosed among more women in the NRT condition than the placebo control (3/203 vs. 1/199).[167] The Coleman trial, however, did not find differences in high blood pressure readings on at least two occasions between study groups and reported slightly fewer cases of preeclampsia/eclampsia in the intervention group (3/521 versus 5/529), although again, event rates were too low to establish a valid association.[168] The two largest 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 one RCT discontinued treatment due to the reaction.[167, 168]

Fetal and infant harms were reported as individual outcomes and composite measures with variable definitions. In the Coleman study, a composite measure of any serious adverse event, defined as any miscarriage, stillbirth, neonatal or post neonatal death, was higher in the NRT intervention group (9/521) vs. placebo (6/529), but precision was too low to assess statistical differences.[168] A composite outcome of any serious adverse event was also reported in the 2008 Oncken trial and included birth outcomes, miscarriage, stillbirth, and neonatal death as well as neonatal or maternal hospitalization.[174] More serious adverse events were observed in the placebo condition than in the intervention group, and the difference approached statistical significance (NRT 24/97, placebo 33/87, p=0.06), with much of the difference attributed to lower rates of preterm birth and low birthweight in the intervention group.[174] A similar composite outcome was reported in the Pollak trial (preterm birth, NICU admissions, small-for gestational age, placenta abruption, fetal demise), with more events found in the intervention group (NRT 30.1%, 34/113 versus placebo 17.2%, 10/58, risk difference 0.13 [95% CI, 0.00 to 0.26]).[176] Adjustment for previous preterm birth narrowed the risk difference (RD=0.09 [95% CI, 0.05 to 0.21]).[176]

In the two larger studies reporting counts of stillbirths, nine occurred in the NRT arms and seven occurred in the placebo control groups (1.3% versus 1.0% respectively).[167, 168] Three trials reported neonatal deaths;[167, 168, 174] there were a total of three cases in the intervention arms and four cases in the control arms in the trials. Congenital malformations were reported in the Berlin and Coleman trials, with fewer cases occurring in the NRT group for both studies (Berlin, NRT 4/203 versus placebo 6/203; Coleman, NRT 9/507 versus placebo 13/517).[167, 168] Between group differences were lower than 1 percent, however, and the confidence intervals crossed null.[167, 168]

The 2-year followup data from the Coleman SNAP trial described for KQ1 did not find evidence of longer-term developmental or respiratory harms associated with NRT use during pregnancy compared with a placebo.[170]

Bupropion – Trial Evidence

We identified no trials that addressed the benefits or harms of bupropion among pregnant women that met our eligibility criteria.

Varenicline – Trial Evidence

We identified no trials that addressed the benefits or harms of varenicline among pregnant women that met our eligibility criteria.

NRT, Bupropion, and Varenicline – Observational Evidence

We included five cohort studies (4 good quality, 1 fair quality), reported in 6 publications, that evaluated the association between gestational use of a smoking cessation medication and risk of adverse fetal and maternal outcomes (**Table 10**).[179-184] Two studies examined exposure to NRT only, one study examined exposure to NRT or bupropion, one study focused on varenicline, and the final study examined exposure to NRT, bupropion, or varenicline. Most studies included two compactors: women who smoked but did not use the cessation medication and non-smoking women or ex-smokers. Here we focus on those who used or were prescribed a smoking cessation medication compared with those who were current smokers. Collectively, there was no evidence of increased risk of premature delivery, small-for-gestational age, stillbirth, congenital anomalies, associated with the use of NRT, bupropion, and varenicline versus smoking.[179-184]

A good quality cohort study using the Quebec Pregnancy cohort data found a lower risk of premature delivery (<37 weeks' gestation) with NRT (adjusted OR, 0.21 [95% CI, 0.13 to 0.34], n=316) and bupropion (adjusted OR, 0.12 [95% CI, 0.03 to 0.50], n=72) compared with women who smoked during pregnancy but did not take either medication (n=900).[179] NRT patch use was associated with a significant reduction in the risk of small for gestational age ($\leq 10^{th}$ percentile for gestational age birthweight) when compared with smoking (adjusted OR, 0.61 [0.41 to 0.90]). Gestational exposure to bupropion was not statistically significantly associated with small for gestational age when compared with smoking (adjusted OR, 0.97 [95% CI, 0.50 to 1.89]).[179]

A fair-quality cohort study conducted in the United Kingdom using the Health Improvement Network database analyzed data from 220,630 singleton pregnancies to assess whether NRT exposure during pregnancy could be associated with stillbirth.[181] A related article reported on congenital anomalies for live-born infants (n=192,498) using the same data source and similar comparisons.[180] Absolute risk of stillbirth was the same (5/1000 births) in women prescribed NRT (n=5221) and those continuing smoking (18,407) and there was no statistically significant difference in the relative risk of stillbirth (adjusted OR, 0.95 [95% CI 0.62 to 1.48]).[181] Similarly, there was no difference in the risk of major congenital anomalies between women prescribed NRT during pregnancy (n=2677) and those who smoked during pregnancy (n=9980) (odds ratio, 1.07 [99% CI, 0.78 to 1.47], p=0.58).[180] There was, however, evidence of an increased risk of respiratory anomalies in the NRT group compared with smokers (OR, 3.49 [99% CI, 1.05 to 11.62], p=0.007), however, this finding was based on only 10 NRT-exposed cases.[180]

Longer-term child health outcomes were also assessed in an included good-quality cohort study using Danish National Birth Cohort data (n=84,803).[184] The study analyzed outcomes for children up to age 14 who were born to women who smoked and for women who used NRT during pregnancy, quit smoking during pregnancy, or did not smoke, and considering whether the father smoked. Diagnosis of attention-deficit hyperactivity disorder (ADHD) after age 5 was the primary outcome. The highest hazard ratio for the development of ADHD during followup

was seen for children whose mothers reported using NRT and had nonsmoking fathers (HR 2.26 [95% CI 1.48 to 3.51]) with a comparison group of nonsmoking mothers and fathers. However, the results are based on small numbers, resulting in wide confidence intervals and unstable estimates. Only seven ADHD cases were identified among children in the NRT group with a smoking father and 22 ADHD cases among children in the NRT group with a nonsmoking father. The estimate was not statistically significant for children with mothers using NRT and fathers who smoked. There also were several differences between the study groups, some accounted for using statistical adjustments, and likely unmeasured confounders that could account for the differences observed.[184]

A large, good-quality cohort study (n=1,017,731) conducted in two states in Australia examined whether use of NRT, bupropion, or varenicline during pregnancy compared with a propensity score-matched unexposed group was associated with risk of adverse perinatal and major congenital anomalies.[183] The risk of any adverse perinatal event was not significantly different between NRT-exposed and unexposed (44.8% vs. 46.3%, hazards ratio [HR] 1.02 [95% CI, 0.84 to 1.23]) and bupropion-exposed and unexposed women (39.2% versus 39.3%, HR 0.93 [95% CI, 0.73 to 1.19]), but it was significantly lower in women exposed to varenicline (36.9% vs. 40.1%, HR 0.86 [95% CI, 0.77 to 0.97]). Additionally, varenicline-exposed infants were less likely than unexposed infants to be born premature, be small for gestational age, and have severe neonatal complications. Among infants exposed to varenicline in the first trimester, 2.9% had a major congenital anomaly vs. 3.5% in unexposed infants (HR 0.91 [95% CI, 0.72 to 1.15]).[183]

Finally, a good-quality population-based cohort study in Denmark and Sweden compared the risk of congenital malformations from birth to the first year of life among infants whose mothers were dispensed varenicline during pregnancy versus infants whose mothers were unexposed to varenicline, but exposed to maternal smoking in utero.[182] Major congenital malformations were detected among 3.6 percent of exposed infants vs. 4.3 percent of unexposed infants (adjusted OR, 0.80 [95% CI 0.545 to 1.42). Furthermore, there was no increased risk of other adverse birth outcomes such as stillbirth, fetal growth restriction, or preterm delivery.[182]

Behavioral Interventions

The Chamberlain review found that behavioral smoking cessation interventions have minimal adverse effects, including the possibility of a paradoxical effect (i.e., increased smoking).[185] Four studies that measured whether women increased their smoking following exposure to the intervention showed mixed results with two studies reporting an increase in smoking behavior among women who did not quit. Thirteen trials reported postintervention psychological outcome measures, and none reported any negative psychological effects. Other potential harms of these interventions were sparsely reported, and none suggested an increase in AEs.[185]

E-Cigarettes

We identified no trials that addressed the harm of e-cigarettes among pregnant women that met our eligibility criteria.

Chapter 4. Discussion

Summary of Evidence

We conducted an overview of reviews to update the evidence on the benefits and harms of tobacco cessation interventions among the general adult population and pregnant adults. This approach allowed us to summarize the evidence on health outcomes, cessation outcomes, and harms of pharmacotherapy (NRT in various forms, bupropion, and varenicline), a variety of primary care-applicable behavioral interventions, and various combinations of pharmacotherapy and behavioral intervention approaches from 67 relevant systematic reviews, with more than 1500 RCTs and observational studies represented. We supplemented the overview of reviews approach with a primary search for studies evaluating the use of e-cigarettes for smoking cessation, given the more recent emergence of this technology and the existing USPSTF determination of insufficient evidence for this approach.[1] Similarly, we conducted a primary search for literature to locate all recent studies related to the use of bupropion among adults given no updated review on the subject and of all pharmacotherapy among pregnant women, given the small evidence base we previously identified and potential harms related to these medications among this population.

The results of our review are consistent with the conclusions of the 2020 Surgeon General's report on Smoking Cessation.[14]

General Adult Population

Available evidence on the impact of tobacco cessation interventions on health outcomes (**KQ 1**) from systematic reviews among general adults represented a single behavioral intervention (physician advice) with no pharmacological treatment (**Table 13**). Our ratings of "low" and "insufficient" for this key question reflect the lack of evidence on health outcomes presented in the included reviews, not a lack of confidence in the beneficial association between quitting smoking and improved health outcomes. The research field has largely moved past the question of whether tobacco cessation interventions improve health outcomes, given that the health benefits of quitting smoking are already firmly established. Within the included reviews, most included studies reported smoking cessation as the primary outcome and emphasized improved validity through biochemical verification of use or more stringent definitions of abstinence.

We have moderate to high confidence that all seven FDA-approved medications for tobacco cessation, a variety of behavioral support and counseling approaches, and the combination of pharmacotherapy plus behavioral support—all interventions that may be readily available to primary care patients and clinicians—can significantly increase the rate of smoking cessation at 6 months and longer compared with usual care or brief self-help materials (**KQ 2**) (**Table 13**). Treatment effects appear to be comparable in a range of populations, settings, and types of behavioral support. Furthermore, despite adding nearly 5 more years of research, the effect estimates for each pooled comparison have been remarkably stable for at least the past three decades (i.e., the time period in which these reviews have been completed and updated).

Analyses of **combined pharmacotherapy and behavioral counseling** interventions suggested an increase in smoking cessation by 68 to 98 percent (RR 1.83) compared with usual care or brief cessation advice or self-help. Likewise, there was clear evidence of effectiveness of pharmacotherapy on smoking abstinence. Based on research involving almost 65,000 smokers, nicotine replacement therapy in any form was effective in increasing relative quit rates by 49 to 61 percent (RR 1.55) compared with placebo or no NRT. A smaller yet still robust body of evidence (27 trials representing over 12,000 smokers) comparing varenicline with placebo found relatively larger effects on smoking cessation (RR 2.24 [95% CI, 2.06 to 2.43]) (defined stringently as 100% biochemically verified continuous abstinence). The absolute differences in mean cessation rates between the medication and control arms was 6.4 percent (16.9% vs. 10.5%), 8.2 percent (19.7% vs. 11.5%), and 14.5 percent (25.6% vs. 11.1%), for NRT, bupropion, and varenicline, respectively. Certain combinations of these medications (e.g., long-term NRT patch plus NRT gum, NRT patch plus bupropion) may also increase quit rates compared with no intervention or a single medication; but fewer trials have tested each combination. Direct comparisons of these drugs, including those with the EAGLES trial,[161] consistently showed that 12 weeks of treatment with varenicline produced higher statistically significant absolute and relative effects on rates of smoking cessation versus NRT and bupropion. No differences have been found between the relative effectiveness of NRT and bupropion in direct or indirect comparisons.

Although often reported as "pharmacotherapy" interventions in our report for brevity, we note that these interventions almost always include some level of behavioral support that is offered to both medication and placebo arms. In trials, the level of behavioral support is often more intense than what is seen in real world settings where most smokers who use cessation medications do not access any type of behavioral support.[29] Robust observational studies have found no relationship between the use of medications and smoking abstinence, especially when not paired with brief advice or behavioral support.[188, 189] The incremental effect of **adding additional behavioral support to pharmacotherapy** versus pharmacotherapy alone or with minimal behavioral support was found to be small but statistically significant (RR, 1.15 [95% CI, 1.08 to 1.22]). In these trials, both arms on medication achieved high rates of quitting (mean quit rates in intervention vs. control, 19.5% vs. 17.1%), and the incremental difference in intensity of the behavioral support between arms was quite modest, about a 0.5 to 5 hours difference in intervention contact time.

Research on **behavioral support interventions** spans a broad range of approaches, including in-person advice and support from health care clinicians or tobacco cessation counselors to a plethora of non-face-to-face formats (tailored and nontailored self-help materials, quitlines, outreach or "proactive" telephone counseling, mobile phone-based interventions, and internet interventions). Compared with various controls, these behavioral interventions produced modest increases in relative smoking cessation at 6 months or more (15% to 88%). Physician or nurse advice, even brief, resulted in a significant relative increase in smoking cessation compared with usual care or self-help materials (RR 1.76 [95% CI, 1.58 to 1.96] and RR 1.29 [95% CI, 1.21 to 1.38], for physician and nurse advice, respectively). These results suggest that there are many effective approaches to aid cessation, and that because of the wide array of options, smokers – with their clinicians – can choose an option that works best for them.

Within and between reviews, there was no strong evidence that specific study, population, or intervention characteristics predicted larger effects or that certain types of behavioral support were more effective than others. The direct evidence on such comparisons was synthesized in many of the reviews but is based on far fewer trials. Furthermore, very few reviews presented direct comparisons of the effects of tobacco cessation interventions between specific subgroups of adults (e.g., those at high risk vs. not at high risk for cardiovascular disease, men vs. women, those with vs. without severe mental illness). Twenty-one reviews summarized the effectiveness of pharmacotherapy and/or behavioral interventions for specific subpopulations of adults (e.g., studies limited to smokeless tobacco users, indigenous populations, those with schizophrenia). None of these reviews suggested findings that differed in direction or magnitude of effects on smoking cessation.

The mean quit rates in the control groups across all the reviews was highly variable, ranging from approximately 5 percent (in trials among smokers receiving usual care in primary care) to approximately 11 to 15 percent (in trials including minimal tobacco cessation behavioral support to control groups). However, the relative effects of the interventions were much less variable and the general absence of substantial heterogeneity between trials within given bodies of evidence makes for reliable estimate of relative effects. If we assume an unassisted quit rate of 5 percent at 12 months in a population of adults attending primary care and use the confidence intervals of interventions using physician advice, 1.58 to 1.96, the result is a number needed to treat (NNT) of 21–34 for additional benefit. If we use the pooled estimate from nurse advice versus usual care, we would decrease the lower confidence interval (1.21) and increase the upper estimate of the NNT to 95. If we assumed a higher quit rate in the usual care control groups (e.g., 10%), less smokers would be needed to treat to see an additional benefit of more intensive advice and/or medications (<20).

There was no evidence of an increased risk of serious AEs, including major cardiovascular AEs and serious neuropsychiatric AEs, among the general adult population associated with NRT, bupropion, or varenicline (**KQ 3**) (**Table 13**). NRT was associated with a higher rate of *any* cardiovascular event, although this was largely driven by low-risk events, typically tachycardia (a well-known risk). Reviews that included AEs related to medication use among individuals with severe mental illness found no difference between study groups in the rates of AEs, including a worsening of psychiatric symptoms or serious psychiatric events (suicide or suicidal ideation).

In contrast to the robust evidence on pharmacotherapy and behavioral interventions for smoking cessation, our review identified only four RCTs that provide data on the use of **e-cigarettes** versus placebo e-cigarettes or NRT for quitting conventional smoking at 6 or more months' followup (**Table 13**). We did not identify any primary evidence on the use of e-cigarettes as tobacco cessation interventions that reported health outcomes. In two of the five trials (n=2008), smokers randomized to e-cigarettes containing nicotine (with or without the co-use of NRT) were found to have statistically significantly greater rates of abstinence than those randomized to NRT alone or NRT plus non-nicotine e-cigarettes at 6- to 12-months followup. In both trials, continued use of e-cigarettes was high at 6- and 12-months followup (~3-9 months after the treatment phase) with 45 to 80 percent of participants still using nicotine-based e-cigarettes as opposed to only 9 to 40 percent of participants still using NRT. Another trial compared the use of

e-cigarettes (two arms using different nicotine concentrations) with placebo at 12 months and found 11 percent abstinence in the nicotine containing e-cigarette groups compared to 4 percent abstinence in the placebo group (p=0.04) but 27 percent of those who quit smoking continued to use e-cigarettes at 1 year. The remaining trial reported no clear difference in the rates of smoking cessation among those randomized to nicotine e-cigarettes versus placebo e-cigarettes at 6 to 12 months' followup. Surprisingly few trials (8 identified in this review) and no large (n>1000) observational cohort studies reported on the potential AEs of e-cigarette use when used to try to quit smoking. This is particularly concerning given the apparent longer-term use of e-cigarettes for cessation compared to pharmacotherapy. The paucity of trial data on AEs related to e-cigarette use is part of the ongoing debate regarding the appropriateness of their use as a cessation tool. However, none of the included trials reported statistically significant differences in rates of serious AEs between intervention and control groups. A 2019 outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI) involving more than 2800 cases, including 68 deaths, is discussed further below.[190]

Pregnant Women

Evidence on the potential benefits and harms of pharmacotherapy for smoking cessation during pregnancy is limited, with few efficacy trials and limited power for detecting both potential benefits and harms (**Table 14**). Our review identified seven trials (five of which were placebo controlled) that evaluated the potential benefits and harms of NRT among pregnant women; our review included no trials evaluating other pharmacotherapies. Across the included trials, there were mixed findings for birth outcomes (**KQ 1**). Only one small trial had statistically significant findings of a benefit across birthweight, low birthweight (<2500 grams) and preterm birth (<37 weeks) outcomes. The largest trial provided evidence from 2-year followup data that survival without impairment was higher with NRT vs. placebo. However a separate study found no association between maternal smoking status and infants' development impairment at 2 years (thus, that there was no evidence of better infant development among infants born to women who were randomized to NRT resulted from smoking cessation induced by nicotine patch use). The trials reported other rare outcomes such as stillbirth but were underpowered for detecting differences in potential adverse consequences of NRT use in pregnancy. Evidence from five large cohort studies did not find differences in stillbirth, birth outcomes, or any congenital anomaly for infants born to mothers with exposure to NRT, bupropion, or varenicline versus those who were unexposed to medications but whose mothers smoked, but incomplete adjustment for confounding limit these findings. Based on the evidence, we could not rule out the possibility of health benefits or of potential harms of smoking cessation medication use in pregnancy.

There was evidence of statistically significant infant health benefits from behavioral tobacco cessation interventions among pregnant women **(KQ 1**). In pooled analyses, the mean birthweight 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 birthweight (<2500g) was also reduced with behavioral interventions. Meta-analysis of the trials reporting preterm birth resulted in statistical uncertainty for the estimate of a small potential benefit of behavioral interventions compared with controls. The number of trials

reporting outcomes and event rates for very low birthweight, stillbirth, and neonatal death was 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 14**). Based on pooled data from trials among over 26,000 women, behavioral interventions were more effective than usual care or minimal support for smoking cessation in late pregnancy (RR 1.35 [95% CI, 1.23 to 1.48]). Although the most common type of intervention was counseling, trials of financial incentive interventions, feedback, and health education had consistent findings of benefit, including some significant individual trials. There was some evidence that the positive effects on smoking cessation in late pregnancy continued into the postpartum period until approximately 18 months postpartum, although the smaller effect sizes show that many women who did quit during pregnancy relapsed postpartum.

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 most trials reported slightly more cessation events in the intervention group. The low adherence to NRT reported in the trials hinders interpretation of the evidence since potential benefits and harms from exposure to NRT are more difficult to discern when exposure is limited and variable.

In terms of potential harms related to NRT cessation interventions used during pregnancy, the available evidence is somewhat reassuring in terms of common health outcomes, such as birthweight, but there was limited power to rule out potential rare harms (**KQ 3**) (**Table 14**). While there was no evidence showing differences in rare outcomes such as miscarriage, stillbirth, and neonatal death, these data are sparse and limited. There was no evidence of AEs related to behavioral interventions among pregnant women.

E-Cigarettes

Laboratory tests of e-cigarette ingredients, in vitro toxicological tests, and short-term human studies suggest that e-cigarettes are likely less harmful in the short-term than combustible tobacco cigarettes. The 2018 National Academies of Sciences, Engineering, and Medicine (National Academies) report on the "Public Health Consequences of E-Cigarettes" concluded that there was substantial evidence that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes.[5] However, due to the lack of long-term epidemiological studies and large clinical trials, the associations between e-cigarette use and morbidity and mortality, especially in the long-term, are not yet clear. Furthermore, much is unknown about their absolute safety profile including concerns about the toxic properties of the variable combination of chemicals present in e-liquids and the additional chemicals generated during the aerosolization of e-liquids.

From August 2019 to February 2020, CDC, the FDA, state and local health departments, and public health and clinical stakeholders investigated a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injury (EVALI).[191] As of February 18, 2020, a total of 2,807

hospitalized cases of EVALI and 68 deaths had been reported to the CDC from all 50 states, the District of Columbia, and 2 U.S. territories (Puerto Rico and U.S. Virgin Islands).[190] The number of EVALI cases reported to CDC peaked during the week of September 15, 2019, and steadily declined since that time.[190]

Laboratory data, including analyses of bronchoalveolar lavage (BAL) fluid samples of patients with EVALI, show that vitamin E acetate was strongly linked to the EVALI outbreak. Vitamin E acetate is an additive in some tetrahydrocannabinol (THC)-containing e-cigarette, or vaping, products.[192] A study analyzed samples from 51 EVALI cases from 16 states and a comparison group of samples from 99 individuals without EVALI for vitamin E acetate and other toxicants; vitamin E acetate was identified in BAL fluid samples from 48 of 51 EVALI patients, but not in the BAL fluid from the comparison group.[192] In an analysis among those hospitalized with EVALI, 82 percent reported using THC-containing products (with 33% reporting exclusive use of THC-containing product) and 57 percent reported using nicotine-containing products (14% was exclusive use of nicotine).[193] National and state data from patient reports and product sample testing showed THC-containing e-cigarette, or vaping, products, particularly from informal sources like friends, or family, or in-person or online dealers, were linked to most of the cases and played a major role in the outbreak.[193] Given this data, the CDC and FDA recommend that people not use THC-containing e-cigarette, or vaping, products, particularly from informal sources like friends, family, or in-person or online dealers[193]. Additionally, CDC and FDA recommend Vitamin E acetate should not be added to any e-cigarette, or vaping, products and people should not add any other substances not intended by the manufacturer to products, including products purchases through retail establishments. CDC recommends that adults using nicotine-containing e-cigarettes or vaping products as an alternative to cigarettes should not go back to smoking; they should weigh all available information and consider using FDA-approved cessation medications.[193] Guidance also suggests that healthcare providers evaluating patients with respiratory symptoms should ask them about e-cigarette, or vaping, product use, evaluate whether they require hospital admission, consider empiric use of antimicrobials, including antivirals, and consider cautious use of corticosteroids.[194] Those hospitalized for EVALI should be followed up, optimally within 48 hours of discharge, to reduce the risk of rehospitalization and death.[195]

Finally, the nicotine in the e-liquid can be hazardous if mishandled and is toxic to children. A national review of over 4000 e-cigarette related poison center calls found that monthly calls regarding e-cigarette exposures in children increased by almost 16 times during the three-year study period. Compared with other tobacco products, children exposed to e-cigarettes had 5.2 times high odds of health care facility admission and 2.6 times higher odds of a severe outcome.[196] Studying the toxicity and safety of e-cigarettes is complicated by the large variation in devices and cartridge fluids available, and the new products rapidly entering the market.

Understanding the public health implications of e-cigarette use at the population level necessitates consideration of not only the risks of e-cigarettes on individual health outcomes, but also the relationship between e-cigarette use and the use of other tobacco products – namely combustible cigarettes. The context surrounding e-cigarette use is markedly different in adolescents and young adults versus middle-aged and older adults. Among high school students, current e-cigarette use fell from 2015 to 2016 before increasing from 2016 to 2017 and

increasing sharply from 2017 to 2018; among middle school students, current e-cigarette use fell from 2015 to 2016 and from 2016 to 2017 before increasing sharply from 2017 to 2018.[197] Some of the main conclusions of the National Academies 2018 report was that there was substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults and moderate evidence that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco cigarette smoking among those who had ever used combustible cigarettes.[5]

The relationship between e-cigarette use and combustible tobacco use among adult smokers could take many pathways, including promoting cessation of combustible cigarette smoking (transitioning to e-cigarette use alone *or* quitting both products), causing former smokers to relapse to combustible smoking after e-cigarette use, or in facilitating dual use of both products simultaneously.[5] Among adults, nearly all e-cigarette users report having started e-cigarette use after having been a regular smoker[198] and most report that quitting smoking and health improvement are major reasons for starting e-cigarettes use.[199, 200] Given what we know about the relative safety of e-cigarettes compared with combustible cigarettes, established combustible tobacco smokers who completely switch to using e-cigarettes would be expected to reduce their tobacco-related health risks. Unfortunately, more than half of adults who report using e-cigarettes also report current smoking.[201] Additional benefit would be expected if e-cigarette users subsequently stopped using both e-cigarettes and combustible tobacco products. Unfortunately, we found no studies meeting inclusion criteria that reported on potential health benefits related to e-cigarette use for quitting smoking among current smokers (**Table 13**). Our review identified five RCTs that examined use of e-cigarettes (with or without NRT) for conventional cigarette cessation at 6 months or longer. Evidence from two recent trials indicated that nicotine-based e-cigarettes (with or without co-use of NRT) may be superior in effectiveness to FDA-approved forms of NRT alone or e-cigarettes that contain no nicotine. The observed self-reported quit rates at 6 months in these two trials varied considerably: one trial reported 35 percent of e-cigarette users (versus 25% in the NRT group) quitting combustible smoking whereas the other reported 18 percent of e-cigarette plus patch users (versus 8% of patch users) quitting smoking. Though the treatment phase in both studies was 12 weeks, more than half of participants continued using e-cigarettes at 6 to 12 months followup, substantially more than subjects who were assigned NRT.

None of the nine trials included in our review to evaluate harms reported any serious AEs considered to be plausibly related to e-cigarette use. Moreover, we found no trials or large cohort studies reporting on long-term health outcomes of e-cigarettes. The paucity of long-term data on AEs and health outcomes related to use is of concern given the recent reports of severe lung injury and the uncertainty about how long persons who use e-cigarettes to quit smoking continue their e-cigarette use even after quitting smoking.

Limitations of the Review

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

The comprehensiveness of our overview 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 Primary results included evidence at least through 2015, there may be evidence on population and intervention subsets that has been published after each review's last search date. If this occurred, the respective bodies of evidence may not reflect 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 overview of reviews.

By adopting an overview 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 did apply scientific judgment 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, 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 considering these potential biases. Although we did not quality-rate the reviews based on the specific choice of meta-analytic models (i.e., random vs. 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. Twenty-seven of the 33 primary reviews were Cochrane reviews. The general consistency and rigor of methods employed by the review authors[202] strengthen this overview of reviews. Furthermore, we quality-rated each review according to AMSTAR 2 criteria[73] 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 among the primary reviews (over 1400). 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 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.

Furthermore, our presentation of results was limited according to the categories of interventions that have been systematically reviewed. That is, we present pooled findings according to categories of interventions that were developed by the systematic reviewers themselves – namely the Cochrane Tobacco Group. While we believe the totality of reviews to reflect the majority of tobacco cessation trials that are applicable to primary care in the United States (e.g., physician advice, nurse advice, group counseling, telephone-based counseling), there still may be applicable tobacco cessation trials that are not represented in any of the source reviews given scoping decisions. Additionally, our reporting of stratified analyses and potential population and intervention effect moderators was limited by the analyses and reporting by included reviews. While most reviews did conduct prespecified stratified analyses and meta-regression, there were few variables that were explored across all reviews.

While we did not re-evaluate the risk of bias within individual trials, several limitations are applicable to all included studies. Biochemical validation of self-reported quitting ranged from less than a quarter of included studies 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 biochemically validated findings 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. Similarly, while results based on point prevalence abstinence and sustained abstinence measures are strongly related and almost always result in similar relative effects, the absolute rates often differ with sustained or continuous abstinence rates averaging around 50 to 70 percent of point prevalence rates.

There is some evidence that industry funding is associated with greater NRT efficacy; but not for bupropion and is less clear for varenicline.[203, 204] This association for NRT may be an indication of a selection bias to publish trials with positive but not negative results. The possibility of small studies effects or potential publication bias is supported by the review we included here that found some evidence of asymmetry in a funnel plot for trials included in the main NRT vs. placebo comparison. Another reasonable explanation, however, is that industry-funded trials often recruit participants who are less likely to quit without medication (heavier smokers) and result in much lower quit rates among control group participants. One review[203] found that industry funding was associated with *lower* odds of quitting smoking among varenicline versus placebo conditions, but the effect was entirely due to two influential trials. Thus, it is somewhat unclear if industry function influences varenicline trials.

Finally, the mechanism by which AEs are recorded (generally passively) makes them susceptible to underreporting. As a result, these findings may be less reliable than for those related to abstinence outcomes.

Applicability

Most of the included studies within each review were conducted in North America and, as such, should be applicable to the U.S. health system. Most studies enrolled only individuals who were smokers who were generally motivated to quit 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 with 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 overview of reviews is very applicable to primary care in the United States. Synthesized information regarding the details of the types of behavioral support represented in this review is provided in **Appendix H** to provide guidance to those wishing to implement smoking cessation interventions.

The available evidence on the use of e-cigarettes to help smokers quit smoking has very low applicability to clinical practice in the United States. Most importantly, giving the rapidly changing landscape of available products (we are currently in the fourth generation of products), the devices that were tested in the included trials are almost all either not available on the market or in the United States anymore or are not being used by most users. Furthermore, within trials, investigators are typically providing specific e-cigarette devices with predefined nicotine doses and schedules; whereas, clinically, we have no guidance on the appropriate devices, delivery of nicotine (e.g., liquid, salt), or dose that would be most effective to prescribe.

Future Research Needs

The findings of these reviews, and the estimated sizes of the treatment effects, have remained remarkably stable over nearly three decades of evidence for the majority of smoking cessation interventions. For instance, in the original Cochrane review on nurse advice to support tobacco cessation published in 1999, 15 studies contributed to the main analysis, with a pooled RR of 1.30 (95% CI, 1.16 to 1.44). The number of studies and participants have more than doubled (now 44 trials and over 20,000 participants) and thus narrowed the CIs but have had very little impact on the point estimate, which in this most recent update is essentially the same as it was in 1999 (RR 1.29 [95% CI, 1.21 to 1.38]). Likewise, the Cochrane review on NRT was first published in 1996. Despite the number of included studies more than doubling over this time, the effect estimate has remained stable (and represents 136 trials) and per the Cochrane Tobacco Addition group, this latest review on NRT compared with placebo will be its final review on this subject. The review states: “In summary, based on 20 years of research and 136 randomized controlled trials in over 64,000 participants, we believe the question of whether NRT helps people to quit smoking to be definitively answered. We consider that further research is highly unlikely to change our confidence in the effect of NRT, and funders and researchers should give careful thought before pursuing further studies comparing established forms of NRT with control.”

This is not to say that all questions about tobacco cessation interventions have been answered. Evidence is still needed to compare different forms, doses, and durations of drugs; to compare drugs with one another; and to test interventions in special populations for which we may reasonably hypothesize that effectiveness differs from that in the general population (e.g., pregnant women, persons with current severe mental illness, those with physical disabilities, nondaily and intermittent smokers), including direct subgroup comparisons. Furthermore, given the promising results of a few trials testing the effectiveness of cytisine and its widespread use in other countries,[205] more research on its effectiveness, comparative effectiveness, and harms are warranted. More trial evidence on the effectiveness of medications to stop smoking with and without behavioral support (including NRT bought over-the-counter) would help elucidate the potential generalizability of the broader evidence base as applied to populations for which intense behavioral support is not being provided or sought alongside medication-based treatment. Additionally, though the evidence has grown over the past 5 years in these areas, more research is warranted on the effectiveness of remotely delivered interventions such as internet- and mobile phone-based interventions. Though a few reviews sought to include trials evaluating tobacco cessation smartphone applications, none were identified that met inclusion criteria. Given the plethora of these programs that are publicly available,[206] future research should be conducted to evaluate their effectiveness on long-term smoking rates. More research is also needed on adapting interventions for diverse populations. Most research in this area has focused on cessation of cigarette smoking. More research is needed on interventions to help people quit other tobacco products such as cigars, smokeless tobacco, and e-cigarettes. Finally, there is a pressing need for future research on relapse prevention to aid in long-term cessation as well as the optional duration of treatment to maximize long-term abstinence.

Given the variation and the limited evidence available from well-designed studies on the association between e-cigarette use and smoking cessation, further research is clearly needed. To definitively answer the question of e-cigarette efficacy for tobacco cessation, trials must compare an e-cigarette intervention with no intervention and with the most effective known combination of pharmacotherapy and behavioral support. Only such a comparative effectiveness study could address how e-cigarette use for cessation compares with known effective intervention. Furthermore, before such research is conducted, additional strategies and research to help standardize and quantify e-cigarette use and nicotine levels is imperative. Future studies should test the more recent generation of products (namely pod mods including JUUL) or the standard research e-cigarette being developed by the National Institute on Drug Abuse and supported through a small business innovation research contract to NJOY.[207] Additionally, research on other new tobacco products, including heated tobacco products such as IQOS and nicotine pouches, which were recently authorized for marketing in the U.S. by the FDA,[208] are encouraged. Studies of older variants of e-cigarettes which are no longer available or not being used by the public are not as helpful in the context of informing clinical practice. Work to understand the types of e-cigarettes and the e-cigarette use patterns, if any, that may be associated with greater success in using e-cigarettes for smoking cessation is needed as is the types, if any, of behavioral support that are associated with greater success in using e-cigarettes for smoking cessation. Research on interventions to help dual users of conventional cigarettes and e-cigarettes quit both products is necessary as is research on potential relapse back to cigarette use among former smokers who use e-cigarettes. Urgent work is needed to better define the causes of acute, severe lung injuries associated with e-cigarette use. Research on the causes

and frequency of poisonings from e-cigarette fluid and injuries from exploding devices is also needed. The long-term health effects of use have not been reported from any study to date. In addition, research is needed to examine the longer-term transition rates of young e-cigarette users to conventional cigarettes and the relapse rates of smokers who have employed e cigarettes as cessation tools. We identified several 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 I Table 1**).

Finally, further research on the effectiveness and safety of cessation medications among pregnant women is warranted. Careful collection of AEs and systems for deriving long-term consequences of exposure during pregnancy is important in future trials, and data on adherence to medications and levels of nicotine exposure from NRT relative to what occurs with smoking would also be valuable. Despite the established importance of medications in aiding cessation in general populations, few studies of pharmacotherapy use have been conducted during pregnancy. For NRT, this is likely due to concerns about the potential harms of nicotine for fetal and child development mostly inferred from animal studies or extrapolated from observed effects of smoking in pregnancy. Since exposure to nicotine is present with smoking, shifting from smoking to NRT during pregnancy could reduce the risk of adverse infant health outcomes known to be caused by smoking. A recent systematic review and meta-analysis provides evidence that the nicotine exposure from standard-dose NRT is lower than the levels seen with smoking.[209] Moreover, if NRT were found to increase the likelihood of long-term cessation after pregnancy, reduced exposure to second-hand smoke during infancy and childhood would further increase the health benefits. Recent evidence of child health benefits from 2-year followup on the largest NRT trial highlight the importance of further research. In the absence of clear evidence that NRT increases cessation in pregnancy, however, it is encouraging that behavioral counseling interventions alone are effective for some women.

For behavioral and NRT interventions, an 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. Others have noted the importance of qualitative and observational research to understand why adherence to NRT in pregnancy is low.[210] 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 the most recent, larger 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, but it is unknown how long-term cessation efforts are affected by this kind of short-term motivation. Different interventions spanning pregnancy, the postpartum period, 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. Unfortunately, we identified few registered studies that appear to address these questions (**Appendix I Table 2**).

Conclusions

There is extensive evidence that confirms the effectiveness of a range of pharmacological and behavioral interventions, alone and in combination, for smoking cessation in adults. Though there has been no decline in the production, sales, or use of e-cigarettes since our previous review on this subject, research on the potential benefits of these devices to help adults quit smoking is still lacking. Furthermore, more research is desperately needed on the absolute safety profile of e-cigarettes and the long-term health consequences of their use among former smokers as well as dual users of both combustible and electronic cigarettes. There is evidence that behavioral interventions can help pregnant women to quit smoking in late pregnancy and into the postpartum period but limited evidence on the benefits and harms of pharmacotherapy in pregnant women.

Further studies of medications and behavioral support among the general adult population are unlikely to yield new information that would change the direction and magnitude of effects of the findings of this overview of reviews. Clinicians have an array of tools to offer, refer, or prescribe, improving the likelihood that patients will find an acceptable option to which they can adhere. Continued research on the evolving landscape of available tobacco products and their role in helping smokers quit combustible cigarette use, along with the long-term risks associated with these products.

References

1. Siu AL, US Preventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163(8):622-34. PMID: 26389730. https://dx.doi.org/10.7326/M15-2023
2. U.S. Food and Drug Administration. FDA's Deeming Regulations for E-Cigarettes, Cigars, and All Other Tobacco Products. https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/fdas-deeming-regulations-e-cigarettes-cigars-and-all-other-tobacco-products#rule. Accessed: 2019.
3. U.S. Food and Drug Administration. Final Rule: Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. Silver Srping, MD: Office of Regulations, Center for Tobacco Products, Food and Drug Administration, HHS; 2016.
4. Goniewicz ML, Kuma T, Gawron M, et al. Nicotine levels in electronic cigarettes. *Nicotine Tob Res*. 2013;15(1):158-66. PMID: 22529223. http://dx.doi.org/10.1093/ntr/nts103
5. National Academies of Sciences, Engineering, and Medicine. Public Health Consequences of E-Cigarettes. Washington, DC: The National Academies Press; 2018.
6. Cohen G, Mehoudar P, Carbonara C, et al. Acute use of nicotine salt-based ends and combusted cigarettes. Presented at: 24th Annual Society for Research on Nicotine and Tobacco (SRNT). February 24, 2018; Baltimore, MD. 2018.
7. Jackler RK, Ramamurthi D. Nicotine arms race: JUUL and the high-nicotine product market. *Tob Control*. 2019;28(6):623-628. PMID: 30733312. https://doi.org/10.1136/tobaccocontrol-2018-054796
8. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tob Control*. 2019;28(2):146-151. PMID: 29853561. http://dx.doi.org/10.1136/tobaccocontrol-2018-054382
9. Etter JF, Bullen C, Flouris AD, et al. Electronic nicotine delivery systems: a research agenda. *Tob Control*. 2011;20(3):243-8. PMID: 21415064. http://dx.doi.org/10.1136/tc.2010.042168
10. Cameron JM, Howell DN, White JR, et al. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. *Tob Control*. 2014;23(1):77-8. PMID: 23407110. http://dx.doi.org/10.1136/tobaccocontrol-2012-050604
11. Trehy ML, Ye W, Hadwiger ME, et al. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. *J Liquid Chromatogr Rel Technol*. 2011;34(14):1442-58. http://dx.doi.org/10.1080/10826076.2011.572213
12. Davis B, Dang M, Kim J, et al. Nicotine concentrations in electronic cigarette refill and do-it-yourself fluids. *Nicotine Tob Res*. 2015;17(2):134-41. PMID: 24862971. http://dx.doi.org/10.1093/ntr/ntu080
13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA: American Psychiatric Association; 2013.

14. U.S. Department of Health and Human Services. Smoking Cessation: A Report of the Surgeon General. Atlanta, GA: 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; 2020.
15. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, et al. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: 2014.
16. Office on Smoking and Health. Women and Smoking: A Report of the Surgeon General. Atlanta, GA: 2001.
17. 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: 2010.
18. World Health Organization. WHO Recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy. Geneva, Switzerland: 2013.
19. Cornelius ME, Wang TW, Jamal A, et al. Tobacco product use among adults - United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69(46):1736-42. PMID: 33211681. https://doi.org/10.15585/mmwr.mm6946a4
20. Obisesan OH, Osei AD, Uddin SMI, et al. Trends in e-cigarette use in adults in the United States, 2016-2018. *JAMA Intern Med*. 2020;180(10):1394-8. PMID: 32897288. https://doi.org/10.1001/jamainternmed.2020.2817
21. Cullen KA, Ambrose BK, Gentzke AS, et al. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students - United States, 2011-2018. *MMWR Morb Mortal Wkly Rep*. 2018;67(45):1276-7. PMID: 30439875. https://doi.org/10.15585/mmwr.mm6745a5
22. Dai H, Leventhal A. Prevalence of e-cigarette use among adults in the United States, 2014-2018. *JAMA*. 2019;322(18):1824-7. PMID: 31524940. https://doi.org/10.1001/jama.2019.15331
23. Drake P, Driscoll AK, Mathews TJ. Cigarette smoking during pregnancy: United States, 2016. *NCHS Data Brief*. 2018(305):1-8. PMID: 29528282.
24. Liu B, Xu G, Rong S, et al. National estimates of e-cigarette use among pregnant and nonpregnant women of reproductive age in the United States, 2014-2017. *JAMA Pediatr*. 2019;173(6):600-602. PMID: 31034001. https://doi.org/10.1001/jamapediatrics.2019.0658
25. Obisesan OH, Osei AD, Uddin SMI, et al. E-cigarette use patterns and high-risk behaviors in pregnancy: Behavioral Risk Factor Surveillance System, 2016-2018. *Am J Prev Med*. 2020;59(2):187-195. PMID: 32362509. https://doi.org/10.1016/j.amepre.2020.02.015
26. DiFranza JR, Savageau JA, Rigotti NA, et al. Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. *Tob Control*. 2002;11(3):228-35. PMID: 12198274. http://dx.doi.org/10.1136/tc.11.3.228
27. Colby SM, Tiffany ST, Shiffman S, et al. Are adolescent smokers dependent on nicotine? A review of the evidence. *Drug Alcohol Depend*. 2000;59 Suppl 1:S83-95. PMID: 10773439. http://dx.doi.org/10.1016/s0376-8716(99)00166-0

28. Fiore MC, Jaen CR, Baker TB. Treating Tobacco Use and Dependence: 2008 Update (Clinical Practice Guideline). *Respir Care*. 2008;53(9):1217-22.
29. Babb S, Malarcher A, Schauer G, et al. Quitting smoking among adults - United States, 2000-2015. *MMWR Morb Mortal Wkly Rep*. 2017;65(52):1457-64. PMID: 28056007. http://dx.doi.org/10.15585/mmwr.mm6552a1
30. Hughes JR, Solomon LJ, Naud S, et al. Natural history of attempts to stop smoking. *Nicotine Tob Res*. 2014;16(9):1190-8. PMID: 24719491. http://dx.doi.org/10.1093/ntr/ntu052
31. Garcia-Rodriguez O, Secades-Villa R, Florez-Salamanca L, et al. Probability and predictors of relapse to smoking: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2013;132(3):479-85. PMID: 23570817. http://dx.doi.org/10.1016/j.drugalcdep.2013.03.008
32. U.S. Food and Drug Administration. Smoking Cessation Products to Help You Quit. U S Department of Health and Human Services [serial on the Internet].
33. Herman AI, Sofuoglu M. Comparison of available treatments for tobacco addiction. *Curr Psychiatry Rep.* 2010;12(5):433-40. PMID: 20623259. http://dx.doi.org/10.1007/s11920-010-0134-6
34. Tutka P, Zatonski W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. *Pharmacol Rep*. 2006;58(6):777-98. PMID: 17220536.
35. Prochaska JJ, Das S, Benowitz NL. Cytisine, the world's oldest smoking cessation aid. *BMJ*. 2013;347:f5198. PMID: 23974638. https://doi.org/10.1136/bmj.f5198
36. World Health Organization. Marketers of electronic cigarettes should halt unproved therapy claims. http://www.who.int/mediacentre/news/releases/2008/pr34/en/.
37. Caponnetto P, Russo C, Bruno CM, et al. Electronic cigarette: a possible substitute for cigarette dependence. *Monaldi Arch Chest Dis*. 2013;79(1):12-9. PMID: 23741941. http://dx.doi.org/10.4081/monaldi.2013.104
38. Wagener TL, Siegel M, Borrelli B. Electronic cigarettes: achieving a balanced perspective. *Addiction*. 2012;107(9):1545-8. PMID: 22471757. http://dx.doi.org/10.1111/j.1360-0443.2012.03826.x
39. Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? *JAMA*. 2014;311(2):135-6. PMID: 24399548. http://dx.doi.org/10.1001/jama.2013.285347
40. Callahan-Lyon P. Electronic cigarettes: human health effects. *Tob Control*. 2014;23 Suppl 2:ii36-ii40. PMID: 24732161. http://dx.doi.org/10.1136/tobaccocontrol-2013-051470
41. Chen IL, Husten CG. Introduction to tobacco control supplement. *Tob Control*. 2014;23 Suppl 2:ii1-ii3. PMID: 24732156. http://dx.doi.org/10.1136/tobaccocontrol-2013-051504
42. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*. 2014;23(2):133-9. PMID: 23467656. http://dx.doi.org/10.1136/tobaccocontrol-2012-050859
43. Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic cigarettes: a policy statement from the American Heart Association. Circulation. 2014;130(16):1418-36. PMID: 25156991. http://dx.doi.org/10.1161/CIR.0000000000000107
44. Tibuakuu M, Okunrintemi V, Jirru E, et al. National trends in cessation counseling, prescription medication use, and associated costs among US adult cigarette smokers.

JAMA Network Open. 2019;2(5):e194585. PMID: 31125108. https://doi.org/10.1001/jamanetworkopen.2019.4585
45. 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;61 Suppl:38-45. PMID: 22695462.
46. 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;98(2):317-22. PMID: 18172143. http://dx.doi.org/10.2105/AJPH.2007.112060
47. 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. http://dx.doi.org/10.1371/journal.pone.0103462
48. Ofei-Dodoo S, Kellerman R, Nilsen K, et al. Family physicians' perceptions of electronic cigarettes in tobacco use counseling. *J Am Board Fam Med*. 2017;30(4):448-59. PMID: 28720626. http://dx.doi.org/10.3122/jabfm.2017.04.170084
49. Nickels AS, Warner DO, Jenkins SM, et al. Beliefs, practices, and self-efficacy of US physicians regarding smoking cessation and electronic cigarettes: a national survey. *Nicotine Tob Res*. 2017;19(2):197-207. PMID: 27613879. http://dx.doi.org/10.1093/ntr/ntw194
50. 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;211(6):695.e1-7. PMID: 24881828. http://dx.doi.org/10.1016/j.ajog.2014.05.041
51. Pepper J, Gilkey M, Brewer N. Physicians' counseling of adolescents regarding e-cigarette use. *J Adolesc Health*. 2015;57(6):580-6. PMID: 26297135. https://doi.org/10.1016/j.jadohealth.2015.06.017
52. Keith DR, Stanton CA, Gaalema DE, et al. Disparities in US healthcare provider screening and advice for cessation across chronic medical conditions and tobacco products. *J Gen Intern Med*. 2017;32(9):974-80. PMID: 28470547. https://doi.org/10.1007/s11606-017-4062-6
53. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel. 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;35(2):158-76. PMID: 18617085 https://doi.org/10.1016/j.amepre.2008.04.009
54. American Medical Association. American Medical Association guidelines for the diagnosis and treatment of nicotine dependence: how to help patients stop smoking. Washington, DC: American Medical Association; 1994.
55. Patel MS, Steinberg MB. In the Clinic. Smoking Cessation. *Ann Intern Med*. 2016;164(5):Itc33-itc48. PMID: 26926702. http://dx.doi.org/10.7326/aitc201603010
56. Larzelere MM, Williams DE. Promoting smoking cessation. *Am Fam Physician*. 2012;85(6):591-8. PMID: 22534270.
57. American Dental Association. Policy and Recommendations on Tobacco Use. Chicago, IL: American Dental Association; 2016.
58. Guide to Community Preventive Services. Tobacco use and secondhand smoke exposure. https://www.thecommunityguide.org/content/2017-annual-report-congress. Accessed: Jan 5, 2017.

59. [No authors listed]. Tobacco and Nicotine Cessation During Pregnancy: ACOG Committee Opinion, Number 807. *Obstet Gynecol*. 2020;135(5):e221-e9. PMID: 32332417. https://doi.org/10.1097/aog.0000000000003822
60. American Academy of Family Physicians. Electronic Nicotine Delivery Systems (ENDS). https://www.aafp.org/about/policies/all/e-cigarettes.html. Accessed: Jan 20, 2020.
61. American College of Obstetricians and Gynecologists. Practice Advisory: Lung Injury Associated with E-cigarettes ("Vaping"). https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Advisories/Lung-Injury-Associated-with-E-cigarettes-Vaping?IsMobileSet=false. Accessed: Jan 20, 2020.
62. American Cancer Society. American Cancer Society Position Statement on Electronic Cigarettes. https://www.cancer.org/healthy/stay-away-from-tobacco/e-cigarette-position-statement.html. Accessed: Jan 20, 2020.
63. Livingston CJ, Freeman RJ, Costales VC, et al. Electronic nicotine delivery systems or e-cigarettes: American College of Preventive Medicine's practice statement. *Am J Prev Med*. 2019;56(1):167-78. PMID: 30573147. https://doi.org/10.1016/j.amepre.2018.09.010
64. National Institute for Health and Care Excellence, Public Health Internal Guideline Development Team. Smoking cessation interventions and services: [C] Evidence reviews for advice on e-cigarettes and general sale. NICE guideline NG92. London, UK: National Institute for Health and Care Excellence; 2018.
65. Brandon TH, Goniewicz ML, Hanna NH, et al. Electronic Nicotine Delivery Systems: A Policy Statement From the American Association for Cancer Research and the American Society of Clinical Oncology. *J Clin Oncol*. 2015;33(8):952-63. PMID: 22572671. https://doi.org/10.1200/JCO.2014.59.4465
66. U.S. Department of Health and Human Services. Surgeon General's Advisory on E-cigarette Use Among Youth. https://e-cigarettes.surgeongeneral.gov/. Accessed: 6/17/2019, 2019.
67. U.S. Department of Health and Human Services, Centers for Diesease Control and Prevention. 2016 Surgeon General's Report: E-Cigarette Use Among Youth and Young Adults. https://www.cdc.gov/tobacco/data_statistics/sgr/e-cigarettes/index.htm. Accessed: 6/17/2019, 2019.
68. 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;150(8):551-5. PMID: 19380855. http://dx.doi.org/10.7326/0003-4819-150-8-200904210-00009
69. 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;283(24):3244-54. PMID: 10866874. https://dx.doi.org/10.1001/jama.283.24.3244
70. Patnode CD, Henderson JT, Thompson JH, et al. 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. *Ann Intern Med*. 2015;163(8):608-21. PMID: 26389650. https://doi.org/10.7326/m15-0171
71. Patnode CD, Henderson JT, Thompson JH, et al. 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. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015.
72. Coleman T, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2015(12):CD010078. PMID: 26690977. https://dx.doi.org/10.1002/14651858.CD010078.pub2
73. Shea BJ, Reeves B, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. PMID: 28935701. https://doi.org/10.1136/bmj.j4008
74. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual. Accessed: May 22, 2019.
75. West R, Hajek P, Stead L, et al. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction*. 2005;100(3):299-303. PMID: 15733243. http://dx.doi.org/10.1111/j.1360-0443.2004.00995.x.
76. Claire R, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2020;3:CD010078. PMID: 32129504. https://doi.org/10.1002/14651858.CD010078.pub3
77. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. *Stat Med*. 2001;20(6):825-40. PMID: 11252006. http://dx.doi.org/10.1002/sim.650
78. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville (MD): Agency for Healthcare Research and Quality; 2014. p. 314-49. PMID: 24404627.
79. Agboola SA, Coleman T, McNeill A, et al. Abstinence and relapse among smokers who use varenicline in a quit attempt-a pooled analysis of randomized controlled trials. *Addiction*. 2015;110(7):1182-93. PMID: 25846123. https://doi.org/10.1111/add.12941
80. Ahmed S, Virani S, Kotapati VP, et al. Efficacy and safety of varenicline for smoking cessation in schizophrenia: a meta-analysis. *Front Psychiatry*. 2018;9:428. PMID: 30283363. https://doi.org/10.3389/fpsyt.2018.00428
81. Apollonio D, Philipps R, Bero L. Interventions for tobacco use cessation in people in treatment for or recovery from substance use disorders. *Cochrane Database Syst Rev*. 2016(11):CD010274. PMID: 27878808. https://doi.org/10.1002/14651858.CD010274.pub2
82. Barnes J, McRobbie H, Dong CY, et al. Hypnotherapy for smoking cessation. *Cochrane Database Syst Rev*. 2019;6:CD001008. PMID: 31198991. https://doi.org/10.1002/14651858.CD001008.pub3
83. Boland VC, Stockings EA, Mattick RP, et al. The methodological quality and effectiveness of technology-based smoking cessation interventions for disadvantaged groups: a systematic review and meta-analysis. *Nicotine Tob Res*. 2016;20(3):276-85. PMID: 28034998. https://doi.org/10.1093/ntr/ntw391
84. Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. *Cochrane Database Syst Rev*. 2014(12):CD008743. PMID: 25547090. https://doi.org/10.1002/14651858.CD008743.pub3

85. Cahill K, Lindson-Hawley N, Thomas KH, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016(5):CD006103. PMID: 27158893. https://doi.org/10.1002/14651858.CD006103.pub7
86. Carson KV, Brinn MP, Peters M, et al. Interventions for smoking cessation in Indigenous populations. *Cochrane Database Syst Rev*. 2012(1):CD009046. PMID: 22258998. http://dx.doi.org/10.1002/14651858.CD009046.pub2
87. Chang PH, Chiang CH, Ho WC, et al. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689. PMID: 26198192. https://doi.org/10.1186/s12889-015-2055-0
88. Clair C, Mueller Y, Livingstone-Banks J, et al. Biomedical risk assessment as an aid for smoking cessation. *Cochrane Database Syst Rev*. 2019(3):CD004705. PMID: 30912847. https://doi.org/10.1002/14651858.CD004705.pub5
89. Danielsson AK, Eriksson AK, Allebeck P. Technology-based support via telephone or web: a systematic review of the effects on smoking, alcohol use and gambling. *Addict Behav*. 2014;39(12):1846-68. PMID: 25128637. https://doi.org/10.1016/j.addbeh.2014.06.007
90. Denison E, Underland V, Mosdol A, et al. Cognitive Therapies for Smoking Cessation: A Systematic Review. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2017.
91. Do HP, Tran BX, Le Pham Q, et al. Which eHealth interventions are most effective for smoking cessation? A systematic review. *Patient Prefer Adherence*. 2018;12:2065-84. PMID: 30349201. https://doi.org/10.2147/ppa.S169397
92. Ebbert JO, Elrashidi MY, Stead LF. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev*. 2015(10):CD004306. PMID: 26501380. https://doi.org/10.1002/14651858.CD004306.pub5
93. Giles E, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis (Structured abstract). *Plos One*. 2014;9(3):e90347. PMID: 24618584. https://doi.org/10.1371/journal.pone.0090347
94. Graham AL, Carpenter KM, Cha S, et al. Systematic review and meta-analysis of internet interventions for smoking cessation among adults. *Subst Abuse Rehabil*. 2016;7:55-69. PMID: 27274333. https://doi.org/10.2147/sar.s101660
95. Hartmann-Boyce J, Hong B, Livingstone-Banks J, et al. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev*. 2019(6):CD009670. PMID: 31166007. https://doi.org/10.1002/14651858.CD009670.pub4
96. Hartmann-Boyce J, Chepkin SC, Ye W, et al. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018(5):CD000146. PMID: 29852054. https://doi.org/10.1002/14651858.CD000146.pub5
97. Hollands GJ, Naughton F, Farley A, et al. Interventions to increase adherence to medications for tobacco dependence. *Cochrane Database Syst Rev*. 2019(8):CD009164. PMID: 31425618. https://doi.org/10.1002/14651858.CD009164.pub3
98. Howes S, Hartmann-Boyce J, Livingstone-Banks J, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2020(4):CD000031. PMID: 32319681. http://dx.doi.org/10.1002/14651858.CD000031.pub5

99. Johnston V, Westphal DW, Glover M, et al. Reducing smoking among indigenous populations: new evidence from a review of trials. *Nicotine Tob Res*. 2013;15(8):1329-38. PMID: 23519776. http://dx.doi.org/10.1093/ntr/ntt022
100. Khanna P, Clifton AV, Banks D, et al. Smoking cessation advice for people with serious mental illness. *Cochrane Database Syst Rev*. 2016(1):CD009704. PMID: 26816385. https://doi.org/10.1002/14651858.CD009704.pub2
101. Kishi T, Iwata N. Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci.* 2015;265(3):259-68. PMID: 25283510. https://doi.org/10.1007/s00406-014-0551-3
102. Klinsophon T, Thaveeratitham P, Sitthipornvorakul E, et al. Effect of exercise type on smoking cessation: a meta-analysis of randomized controlled trials. *BMC Res Notes*. 2017;10(1):442. PMID: 28874175. https://doi.org/10.1186/s13104-017-2762-y
103. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev*. 2017(3):CD001292. PMID: 28361496. https://doi.org/10.1002/14651858.CD001292.pub3
104. Lindson N, Chepkin S, Ye W, et al. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2019(4):CD013308. https://doi.org/10.1002/14651858.CD013308
105. Lindson N, Klemperer E, Hong B, et al. Smoking reduction interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019(9):CD013183. PMID: 31565800. https://doi.org/10.1002/14651858.CD013183.pub2
106. Lindson N, Thompson TP, Ferrey A, et al. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*. 2019(7):CD006936. PMID: 31425622. https://doi.org/10.1002/14651858.CD006936.pub4
107. Liu JJ, Wabnitz C, Davidson E, et al. Smoking cessation interventions for ethnic minority groups: a systematic review of adapted interventions. *Prev Med*. 2013;57(6):765-75. PMID: 24076130. http://dx.doi.org/10.1016/j.ypmed.2013.09.014
108. Livingstone-Banks J, Norris E, Hartmann-Boyce J, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019(2):CD003999. PMID: 30758045. https://doi.org/10.1002/14651858.CD003999.pub5
109. Livingstone-Banks J, Ordonez-Mena JM, Hartmann-Boyce J. Print-based self-help interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019(1):CD001118. PMID: 30623970. https://doi.org/10.1002/14651858.CD001118.pub4
110. Matkin W, Ordonez-Mena JM, Hartmann-Boyce J. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev*. 2019(5):CD002850. PMID: 31045250. https://doi.org/10.1002/14651858.CD002850.pub4
111. McCrabb S, Baker AL, Attia J, et al. Internet-based programs incorporating behavior change techniques are associated with increased smoking cessation in the general population: a systematic review and meta-analysis. *Ann Behav Med*. 2019;53(2):180-95. PMID: 29750240. https://doi.org/10.1093/abm/kay026
112. McKee SA, Smith PH, Kaufman M, et al. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. *Nicotine Tob Res.* 2016;18(5):1002-11. PMID: 26446070. https://doi.org/10.1093/ntr/ntv207
113. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation*. 2014;129(1):28-41. PMID: 24323793. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.003961

114. 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. http://dx.doi.org/10.1186/1617-9625-8-8
115. Moyo F, Archibald E, Slyer JT. Effectiveness of decision aids for smoking cessation in adults: a quantitative systematic review. *JBI Database System Rev Implement Rep*. 2018;16(9):1791-822. PMID: 30204670. https://doi.org/10.11124/jbisrir-2017-003698
116. Notley C, Gentry S, Livingstone-Banks J, et al. Incentives for smoking cessation. *Cochrane Database Syst Rev*. 2019(7):CD004307. PMID: 31313293. https://doi.org/10.1002/14651858.CD004307.pub6
117. Palmer M, Sutherland J, Barnard S, et al. The effectiveness of smoking cessation, physical activity/diet and alcohol reduction interventions delivered by mobile phones for the prevention of non-communicable diseases: a systematic review of randomised controlled trials. *PLoS One*. 2018;13(1):e0189801. PMID: 29304148. https://doi.org/10.1371/journal.pone.0189801
118. Peckham E, Brabyn S, Cook L, et al. Smoking cessation in severe mental ill health: what works? An updated systematic review and meta-analysis. *BMC Psychiatry*. 2017;17(1):252. PMID: 28705244. https://doi.org/10.1186/s12888-017-1419-7
119. Rice VH, Heath L, Livingstone-Banks J, et al. Nursing interventions for smoking cessation. *Cochrane Database Syst Rev*. 2017(12):CD00118. PMID: 29243221. https://doi.org/10.1002/14651858.CD001188.pub5
120. Roberts E, Evins A, McNeill A, et al. Efficacy and tolerability of pharmacotherapy for smoking cessation in adults with serious mental illness: a systematic review and network meta-analysis. *Addiction*. 2016;111(4):599-612. PMID: 26594837. http://dx.doi.org/10.1111/add.13236
121. Rosen LJ, Galili T, Kott J, et al. Diminishing benefit of smoking cessation medications during the first year: a meta-analysis of randomized controlled trials. *Addiction*. 2018;113(5):805-16. PMID: 29377409. https://doi.org/10.1111/add.14134
122. Schuit E, Panagiotou OA, Munafo MR, et al. Pharmacotherapy for smoking cessation: effects by subgroup defined by genetically informed biomarkers. *Cochrane Database Syst Rev*. 2017(9):CD011823. PMID: 28884473. https://doi.org/10.1002/14651858.CD011823.pub2
123. Schwartz J, Fadahunsi O, Hingorani R, et al. Use of varenicline in smokeless tobacco cessation: a systematic review and meta-analysis. *Nicotine Tob Res*. 2016;18(1):10-6. PMID: 25646351. https://doi.org/10.1093/ntr/ntv010
124. Smith PH, Weinberger AH, Zhang J, et al. Sex differences in smoking cessation pharmacotherapy comparative efficacy: a network meta-analysis. *Nicotine Tob Res*. 2016;19(3):273-81. https://doi.org/10.1093/ntr/ntw144
125. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. *Cochrane Database Syst Rev*. 2013(5):CD000165. PMID: 23728631. http://dx.doi.org/10.1002/14651858.CD000165.pub4
126. Stead LF, Carroll AJ, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database Syst Rev*. 2017(3):CD00107. PMID: 28361497. https://doi.org/10.1002/14651858.CD001007.pub3

127. Stead LF, Koilpillai P, Fanshawe TR, et al. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2016(3):CD008286. PMID: 27009521. https://doi.org/10.1002/14651858.CD008286.pub3
128. Sterling LH, Windle SB, Filion KB, et al. Varenicline and adverse cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2016;5(2):e002849. PMID: 26903004. https://doi.org/10.1161/jaha.115.002849
129. Taylor GM, Dalili MN, Semwal M, et al. Internet-based interventions for smoking cessation. *Cochrane Database Syst Rev*. 2017(9):CD007078. PMID: 28869775. https://doi.org/10.1002/14651858.CD007078.pub5
130. Thomas D, Abramson MJ, Bonevski B, et al. System change interventions for smoking cessation. *Cochrane Database Syst Rev*. 2017(2):CD010742. PMID: 28185257. https://doi.org/10.1002/14651858.CD010742.pub2
131. Thomas KH, Martin RM, Knipe DW, et al. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. *BMJ*. 2015;350:h1109. PMID: 25767129. http://dx.doi.org/10.1136/bmj.h1109
132. Thurgood SL, McNeill A, Clark-Carter D, et al. A systematic review of smoking cessation interventions for adults in substance abuse treatment or recovery. *Nicotine Tob Res*. 2016;18(5):993-1001. PMID: 26069036. http://dx.doi.org/10.1093/ntr/ntv127
133. 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. http://dx.doi.org/10.1002/14651858.CD007253.pub3
134. Tzelepis F, Paul CL, Williams CM, et al. Real-time video counselling for smoking cessation. *Cochrane Database Syst Rev*. 2019(10):CD012659. PMID: 31684699. https://doi.org/10.1002/14651858.CD012659.pub2
135. Ussher MH, Faulkner GE, Angus K, et al. Exercise interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019(10):CD002295. PMID: 31684691. https://doi.org/10.1002/14651858.CD002295.pub6
136. 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. http://dx.doi.org/10.1002/14651858.CD006102.pub2
137. White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. *Cochrane Database Syst Rev*. 2014(1):CD000009. PMID: 24459016. http://dx.doi.org/10.1002/14651858.CD000009.pub4
138. Whittaker R, McRobbie H, Bullen C, et al. Mobile phone text messaging and app-based interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019(10):CD006611. PMID: 31638271. https://doi.org/10.1002/14651858.CD006611.pub5
139. Wilson A, Guillaumier A, George J, et al. A systematic narrative review of the effectiveness of behavioural smoking cessation interventions in selected disadvantaged groups (2010-2017). *Expert Rev Respir Med*. 2017;11(8):617-30. PMID: 28608758. https://doi.org/10.1080/17476348.2017.1340836
140. Windle SB, Filion KB, Mancini JG, et al. Combination therapies for smoking cessation: a hierarchical Bayesian meta-analysis. *Am J Prev Med*. 2016;51(6):1060-71. PMID: 27617367. https://doi.org/10.1016/j.amepre.2016.07.011
141. Wu L, Sun S, He Y, et al. Effect of smoking reduction therapy on smoking cessation for smokers without an intention to quit: an updated systematic review and meta-analysis of

randomized controlled trial. *Int J Environ Res Public Health*. 2015;12(9):10235-53. PMID: 26308034. https://doi.org/10.3390/ijerph120910235
142. Wu Q, Gilbody S, Peckham E, et al. Varenicline for smoking cessation and reduction in people with severe mental illnesses: systematic review and meta-analysis. *Addiction*. 2016;111(9):1554-67. PMID: 27043328. https://doi.org/10.1111/add.13415
143. Bullen C, Williman J, Howe C, et al. Study protocol for a randomised controlled trial of electronic cigarettes versus nicotine patch for smoking cessation. *BMC Public Health*. 2013;13:210. PMID: 23496861. https://doi.org/10.1186/1471-2458-13-210
144. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382(9905):1629-37. PMID: 24029165. https://doi.org/10.1016/S0140-6736(13)61842-5
145. 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. https://doi.org/10.1371/journal.pone.0066317
146. Masiero M, Lucchiari C, Mazzocco K, et al. E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: preliminary results by randomized controlled trial. *Nicotine Tob Res*. 2019;21(1):119-26. PMID: 29660034. https://doi.org/10.1093/ntr/nty047
147. Carpenter MJ, Heckman BW, Wahlquist AE, et al. A naturalistic, randomized pilot trial of e-cigarettes: uptake, exposure, and behavioral effects. *Cancer Epidemiol Biomarkers Prev*. 2017;26(12):1795-803. PMID: 29127080. https://doi.org/10.1158/1055-9965.epi-17-0460
148. Cravo AS, Bush J, Sharma G, et al. A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. *Regul Toxicol Pharmacol*. 2016;81(Suppl 1):S1-s14. PMID: 27769828. https://doi.org/10.1016/j.yrtph.2016.10.003
149. Lucchiari C, Masiero M, Veronesi G, et al. Benefits of e-cigarettes among heavy smokers undergoing a lung cancer screening program: randomized controlled trial protocol. *JMIR Res Protocols*. 2016;5(1):e21. PMID: 26842790. https://doi.org/10.2196/resprot.4805
150. Tseng TY, Ostroff JS, Campo A, et al. A randomized trial comparing the effect of nicotine versus placebo electronic cigarettes on smoking reduction among young adult smokers. *Nicotine Tob Res*. 2016;18(10):1937-43. PMID: 26783292. https://doi.org/10.1093/ntr/ntw017
151. O'Brien B, Knight-West O, Walker N, et al. E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. *Tob Induc Dis*. 2015;13(1):5. PMID: 25814920. https://doi.org/10.1186/s12971-015-0030-2
152. Bullen C, Howe C, Laugesen M. Electronic cigarettes for smoking cessation: a randomised controlled trial. *J Vasc Surg*. 2014;59(3):872. https://doi.org/10.1016/j.jvs.2014.01.028
153. Caponnetto P, Campagna D, Cibella F, et al. Erratum: EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*. 2014;9(1). https://doi.org/10.1371/annotation/e12c22d3-a42b-455d-9100-6c7ee45d58d0

154. Hajek P, Phillips-Waller A, Przulji D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380(629-37). PMID: 30699054. https://doi.org/10.1056/NEJMoa1808779
155. Walker N, Parag V, Verbiest M, et al. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respir Med*. 2020;8(1):54-64. PMID: 31515173. https://doi.org/10.1016/S2213-2600(19)30269-3
156. Hajek P, Phillips-Waller A, Przulj D, et al. E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: the TEC RCT. *Health Technol Assess*. 2019;23(43):1-82. PMID: 31434605. https://dx.doi.org/10.3310/hta23430
157. Lee SH, Ahn SH, Cheong YS. Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: a randomized controlled study. *J Am Board Fam Med*. 2019;32(4):567-74. PMID: 31300577. https://doi.org/10.3122/jabfm.2019.04.180384
158. Masiero M, Lucchiari C, Mazzocco K, et al. Corrigendum: e-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: preliminary results by randomized controlled trial. *Nicotine Tob Res*. 2020;22(4):594-5. https://doi.org/10.1093/ntr/nty175
159. 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;32(4):275-81. PMID: 370171. http://dx.doi.org/10.1136/jech.32.4.275
160. Rose G, Colwell L. Randomised controlled trial of anti-smoking advice: final (20 year) results. *J Epidemiol Community Health*. 1992;46(1):75-7. PMID: 1573365. http://dx.doi.org/10.1016/j.amepre.2007.05.006
161. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387(10037):2507-20. PMID: 27116918. https://doi.org/10.1016/S0140-6736(16)30272-0
162. Miller W, Rollnick S. Motivational Interviewing: Preparing People for Change. New York: Guildfort Press; 2002.
163. American Lung Association. Freedom from Smoking. http://www.freedomfromsmoking.org/. Accessed: 5/17/2019, 2019.
164. Benowitz NL, Pipe A, West R, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):622-31. PMID: 29630702. https://doi.org/10.1001/jamainternmed.2018.0397
165. Evins AE, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with psychotic, anxiety, and mood disorders in the EAGLES trial. *J Clin Psychopharmacol*. 2019;39(2):108-16. PMID: 30811371. https://dx.doi.org/10.1097/JCP.0000000000001015
166. Cahill K, Hartmann-Boyce J, Perera R. Incentives for smoking cessation. *Cochrane Database Syst Rev*. 2015(5):CD004307. PMID: 25983287. https://doi.org/10.1002/14651858.CD004307.pub5

167. 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. http://dx.doi.org/10.1136/bmj.g1622
168. Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. *New Engl J Med*. 2012;366(9):808-18. PMID: 22375972. http://dx.doi.org/10.1056/NEJMoa1109582
169. Cooper S, Lewis S, Thornton JG, et al. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy--clinical effectiveness and safety until 2 years after delivery, with economic evaluation. *Health Technol Assess*. 2014;18(54):1-128. PMID: 25158081. https://dx.doi.org/10.3310/hta18540
170. 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. *Lancet Respir Med*. 2014(9):728-37. PMID: 25127405. http://dx.doi.org/10.1016/S2213-2600(14)70157-2
171. El-Mohandes AA, Windsor R, Tan S, et al. A randomized clinical trial of trans-dermal nicotine replacement in pregnant African-American smokers. *Matern Child Health J*. 2013;17(5):897-906. PMID: 22761006. http://dx.doi.org/10.1007/s10995-012-1069-9
172. Essex HN, Parrott S, Wu Q, et al. Cost-effectiveness of nicotine patches for smoking cessation in pregnancy: a placebo randomized controlled trial (SNAP). *Nicotine Tob Res*. 2015;17(6):636-42. PMID: 25481916. https://dx.doi.org/10.1093/ntr/ntu258
173. Iyen B, Vaz LR, Taggar J, et al. Is the apparently protective effect of maternal nicotine replacement therapy (NRT) used in pregnancy on infant development explained by smoking cessation?: secondary analyses of a randomised controlled trial. *BMJ Open*. 2019;9(7):e024923. PMID: 31300493. https://dx.doi.org/10.1136/bmjopen-2018-024923
174. Oncken C, Dornelas E, Greene J, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. *Obstet Gynecol*. 2008;112(4):859-67. PMID: 18827129. http://dx.doi.org/10.1097/AOG.0b013e318187e1ec
175. Oncken C, Dornelas EA, Kuo CL, et al. Randomized trial of nicotine inhaler for pregnant smokers. *Am J Obstet Gynecol MFM*. 2019;1(1):10-8. PMID: 31380506. http://dx.doi.org/10.1016/j.ajogmf.2019.03.006
176. Pollak KI, Oncken CA, Lipkus IM, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. *Am J Prev Med*. 2007;33(4):297-305. PMID: 17888856. http://dx.doi.org/10.1016/j.amepre.2007.05.006
177. Vaz LR, Coleman T, Cooper S, et al. The Nicotine metabolite ratio in pregnancy measured by trans-3'-hydroxycotinine to cotinine ratio: characteristics and relationship with smoking cessation. *Nicotine Tob Res*. 2015;17(11):1318-23. PMID: 25589677. https://dx.doi.org/10.1093/ntr/ntu342
178. Wisborg K, Henriksen TB, Jespersen LB, et al. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstet Gynecol*. 2000;96(6):967-71. PMID: 11084187. http://dx.doi.org/10.1016/s0029-7844(00)01071-1
179. Berard A, Zhao JP, Sheehy O. Success of smoking cessation interventions during pregnancy. *Am J Obstet Gynecol*. 2016;215(5):611.e1-.e8. PMID: 27402053. https://dx.doi.org/10.1016/j.ajog.2016.06.059
180. Dhalwani NN, Szatkowski L, Coleman T, et al. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. *Pediatrics*. 2015;135(5):859-67. PMID: 25847803. http://dx.doi.org/10.1542/peds.2014-2560

181. Dhalwani NN, Szatkowski L, Coleman T, et al. Stillbirth among women prescribed nicotine replacement therapy in pregnancy: analysis of a large UK pregnancy cohort. *Nicotine Tob Res*. 2018;21(4):409-15. PMID: 29394405. https://doi.org/10.1093/ntr/nty019
182. Pedersen L, Petronis KR, Norgaard M, et al. Risk of adverse birth outcomes after maternal varenicline use: a population-based observational study in Denmark and Sweden. *Pharmacoepidemiol Drug Saf*. 2020;29(1):94-102. PMID: 31713302. https://dx.doi.org/10.1002/pds.4894
183. Tran DT, Preen DB, Einarsdottir K, et al. Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study. *BMC Medicine*. 2020;18(1):15. PMID: 32019533. https://dx.doi.org/10.1186/s12916-019-1472-9
184. Zhu JL, Olsen J, Liew Z, et al. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. *Pediatrics*. 2014;134(2):e382-8. PMID: 25049343. https://dx.doi.org/10.1542/peds.2014-0213
185. Chamberlain C, O'Mara-Eves A, Porter J, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev*. 2017(2):CD00105. PMID: 28196405. https://doi.org/10.1002/14651858.CD001055.pub5
186. Griffiths SE, Parsons J, Naughton F, et al. Are digital interventions for smoking cessation in pregnancy effective? A systematic review and meta-analysis. *Health Psychol Rev*. 2018;12(4):333-56. PMID: 29912621. https://doi.org/10.1080/17437199.2018.1488602
187. Wilson SM, Newins AR, Medenblik AM, et al. Contingency management versus psychotherapy for prenatal smoking cessation: a meta-analysis of randomized controlled trials. *Womens Health Issues*. 2018;28(6):514-23. PMID: 30061033. https://doi.org/10.1016/j.whi.2018.05.002
188. Leas EC, Pierce JP, Benmarhnia T, et al. Effectiveness of pharmaceutical smoking cessation aids in a nationally representative cohort of American smokers. *J Natl Cancer Inst*. 2018;110(6):581-7. PMID: 29281040. http://dx.doi.org/10.1093/jnci/djx240
189. Brown J, Beard E, Kotz D, et al. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction*. 2014;109(9):1531-40. http://dx.doi.org/10.1111/add.12623
190. Krishnasamy VP, Hallowell BD, Ko JY, et al. Update: characteristics of a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury - United States, August 2019-January 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(3):90-4. PMID: 31971931. https://doi.org/10.15585/mmwr.mm6903e2
191. Moritz ED, Zapata LB, Lekiachvili A, et al. Update: characteristics of patients in a national outbreak of e-cigarette, or vaping, product use-associated lung injuries - United States, October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(43):985-9. PMID: 31671085. http://dx.doi.org/10.15585/mmwr.mm6843e1
192. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *N Engl J Med*. 2019;382(8):697-705. PMID: 31860793. https://doi.org/10.1056/NEJMoa1916433
193. Office on Smoking and Health. Outbreak of Lung Injury Associated with E-Cigarette Use, or Vaping. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html.

194. Jatlaoui TC, Wiltz JL, Kabbani S, et al. Update: interim guidance for health care providers for managing patients with suspected e-cigarette, or vaping, product use-associated lung injury - United States, November 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(46):1081-6. PMID: 31751322. http://dx.doi.org/10.15585/mmwr.mm6846e2
195. Evans ME, Twentyman E, Click ES, et al. Update: interim guidance for health care professionals evaluating and caring for patients with suspected e-cigarette, or vaping, product use-associated lung injury and for reducing the risk for rehospitalization and death following hospital discharge - United States, December 2019. *MMWR Morb Mortal Wkly Rep*. 2020;68(5152):1189-94. PMID: 31895915. https://doi.org/10.15585/mmwr.mm685152e2
196. Kamboj A, Spiller HA, Casavant MJ, et al. Pediatric exposure to e-cigarettes, nicotine, and tobacco products in the United States. *Pediatrics*. 2016;137(6). PMID: 27244861. http://dx.doi.org/10.1542/peds.2016-0041
197. Gentzke AS, Creamer M, Cullen KA, et al. Vital Signs: tobacco product use among middle and high school students - United States, 2011-2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):157-64. PMID: 30763302. https://doi.org/10.15585/mmwr.mm6806e1
198. Centers for Disease Control and Prevention. QuickStats: Cigarette Smoking Status* Among Current Adult E-cigarette Users,(dagger) by Age Group - National Health Interview Survey,(section sign) United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(42):1177. PMID: 27787495. http://dx.doi.org/10.15585/mmwr.mm6542a7
199. Patel D, Davis KC, Cox S, et al. Reasons for current E-cigarette use among U.S. adults. *Prev Med*. 2016;93:14-20. PMID: 27612572. http://dx.doi.org/10.1016/j.ypmed.2016.09.011
200. Zhuang YL, Cummins SE, Sun JY, et al. Long-term e-cigarette use and smoking cessation: a longitudinal study with US population. *Tob Control*. 2016;25(Suppl 1):i90-i5. PMID: 27697953. http://dx.doi.org/10.1136/tobaccocontrol-2016-053096
201. [No authors listed]. QuickStats: Cigarette Smoking Status* Among Current Adult E-cigarette Users,(†) by Age Group - National Health Interview Survey,(§) United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(42):1177. PMID: 27787495. https://doi.org/10.15585/mmwr.mm6542a7
202. Cochrane Tobacco Addiction Group. Cochrane Tobacco Addiction Group's website. https://tobacco.cochrane.org/. Accessed: May 20, 2019, 2019.
203. Klemperer EM, Hughes JR, Naud S. Study characteristics influence the efficacy of substance abuse treatments: a meta-analysis of medications for smoking cessation. *Nicotine Tob Res*. 2020;22(3):317-323. PMID: 30380134. http://dx.doi.org/10.1093/ntr/nty225
204. Etter JF, Burri M, Stapleton J. The impact of pharmaceutical company funding on results of randomized trials of nicotine replacement therapy for smoking cessation: a meta-analysis. *Addiction*. 2007;102(5):815-22. PMID: 17493109. http://dx.doi.org/10.1111/j.1360-0443.2007.01822.x
205. Tutka P, Vinnikov D, Courtney RJ, et al. Cytisine for nicotine addiction treatment: a review of pharmacology, therapeutics and an update of clinical trial evidence for smoking cessation. *Addiction*. 2019;[Epub ahead of print]. PMID: 31240783. https://doi.org/10.1111/add.14721

206. Haskins BL, Lesperance D, Gibbons P, et al. A systematic review of smartphone applications for smoking cessation. *Transl Behav Med*. 2017;7(2):292-9. PMID: 28527027. https://doi.org/10.1007/s13142-017-0492-2
207. National Institute on Drug Abuse. Supplemental Information for NIDA e-cig. https://www.drugabuse.gov/funding/nida-funding-opportunities/supplemental-information-nida-e-cig. Accessed: Jul 24, 2020.
208. Food and Drug Administration. FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information. Food and Drug Administration; 2020.
209. Hickson C, Lewis S, Campbell KA, et al. Comparison of nicotine exposure during pregnancy when smoking and abstinent with nicotine replacement therapy: systematic review and meta-analysis. *Addiction.* 2019;114(3):406-24. PMID: 30315598. http://dx.doi.org/10.1111/add.14473
210. Coleman T, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2012(9):CD010078. PMID: 22972148. http://dx.doi.org/10.1002/14651858.CD010078
211. Hughes JR, Stead LF, Hartmann BJ, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014(1):CD000031. PMID: 24402784. http://dx.doi.org/10.1002/14651858.CD000031.pub4
212. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed: December 3, 2018.
213. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*. 2015;3:CD006936. PMID: 25726920. http://dx.doi.org/10.1002/14651858.CD006936.pub3

Figure 1. Analytic Framework

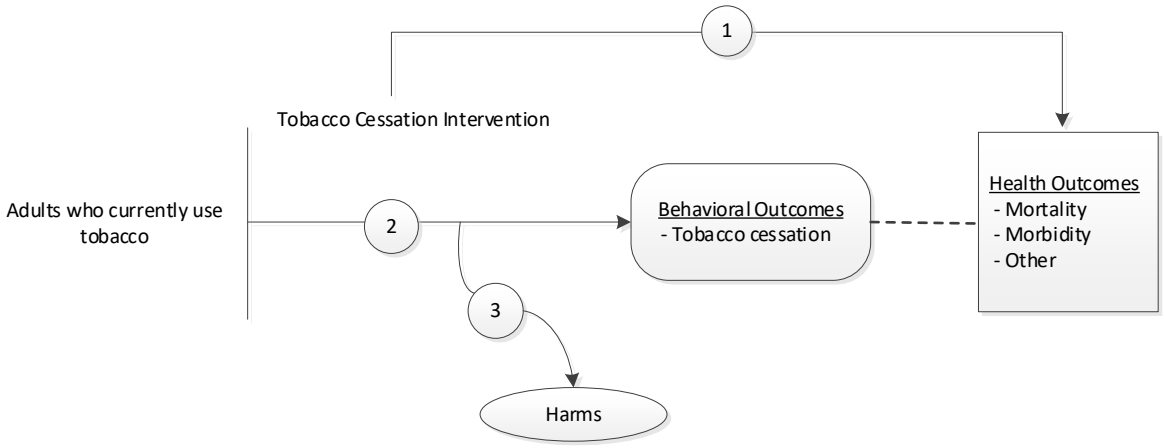

Table 1. U.S. Preventive Services Task Force Summary of Recommendations for Tobacco Cessation in Adults

Population	Recommendation	Grade
Adults who are not pregnant	The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and U.S. Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco.	A
Pregnant women	The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco.	A
Pregnant women	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women.	I
All adults, including pregnant women	The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety (previously stated).	I

Table 2. Characteristics of Included Systematic Reviews by Review Focus, Intervention, and Last Search Date

Focus (Number of reviews)	Author, Year	Primary review*	Quality†	Specific intervention or subgroup	Last search date	Total # of included studies	KQ 1: Health outcomes	KQ 2: Cessation	KQ 3: Harms
Benefits of combined pharmacotherapy and behavioral support (1 review)	Stead, 2016[127]	X	Moderate	Combined pharmacotherapy and behavioral support	July-2015	53		X	
Benefits and harms of pharmacotherapy (13 reviews)	Hartmann-Boyce, 2018[96]	X	High	NRT	July-2017	136		X	X
	Lindson, 2019a[104]	X	High	NRT, different doses, durations, and combinations	Apr-2018	63		X	X
	Mills, 2010[114]‡	X	Moderate	NRT (Harms only)	Nov-2009	120			X
	Howes, 2020[98]	X	High	Bupropion	April-2019	115		X	X
	Cahill, 2016[85]	X	Moderate	Varenicline	May-2015	44		X	X
	Agboola, 2015[79]		Low	Varenicline	Sept-2013	19		X	
	Sterling, 2016[128]	X	Low	Varenicline (Harms only)	June-2015	38			X
	Thomas, 2015[131]	X	High	Varenicline (Harms only)	May-2014	44			X
	Chang, 2015[87]	X	Moderate	Varenicline + NRT	Nov-2014	3		X	X
	Windle, 2016[140]		Moderate	NRT, bupropion, varenicline	July-2015	123		X	X
	Mills, 2014[113]‡	X	Moderate	NRT, bupropion, varenicline (Harms only)	Mar-2013	63			X
	Rosen, 2018[121]		Low	NRT, bupropion, varenicline	Dec-11, July-12, July-13	61		X	
	Hollands, 2019[97]	X	High	Support for medication adherence	Sept-2018	10		X	X
Benefits and harms of behavioral interventions (25 reviews)	Hartmann-Boyce, 2019[95]	X	High	Behavioral support as an adjunct to pharmacotherapy	June-2018	83		X	
	Stead, 2013[125]‡	X	High	Physician advice	Jan-2013	42	X	X	
	Rice, 2017[119]	X	High	Nurse support	Jan-2017	59		X	
	Lancaster, 2017[103]	X	High	Individual behavioral counseling	May-2016	49		X	
	Stead, 2017[126]	X	Moderate	Group behavioral therapy	May-2016	66		X	
	Lindson, 2019b [106]	X	High	Motivational interviewing	Aug-2018	37		X	
	Denison, 2017[90]		Moderate	Cognitive therapy	Nov-2016	21		X	
	Moyo, 2018[115]	X	Moderate	Decision aids	July-2017	7		X	
	Livingstone-Banks, 2019b[109]	X	Moderate	Print-based interventions	Mar-2018	75		X	
	Matkin, 2019[110]	X	Moderate	Telephone counseling	May-2018	104		X	
	Danielsson, 2014[89]		Low	Telephone- or internet-based support	May-2013	74		X	
	Tzelepis, 2019[134]	X	High	Real-time video counseling	Aug-2019	2		X	
	Palmer, 2018[117]		Moderate	Mobile phone-based support	Jan-2016	18		X	
	Whittaker, 2019[138]	X	High	Mobile phone text messaging and app-	Oct-2018	26		X	

Table 2. Characteristics of Included Systematic Reviews by Review Focus, Intervention, and Last Search Date

Focus (Number of reviews)	Author, Year	Primary review*	Quality†	Specific intervention or subgroup	Last search date	Total # of included studies	KQ 1: Health outcomes	KQ 2: Cessation	KQ 3: Harms
				based interventions					
	Do, 2018[91]		Moderate	Mobile phone- and Internet-based interventions	Mar-2017	108		X	
	McCrabb, 2019[111]		Moderate	Internet-based interventions	Sept-2017	45		X	
	Taylor, 2017[129]	X	High	Internet-based interventions	Aug-2016	77		X	X
	Graham, 2016[94]		Moderate	Internet-based interventions	Apr-2015	40		X	
	Notley, 2019[116]	X	High	Incentives	July-2018	33		X	X
	Giles, 2014[93]		Moderate	Financial-based incentives	Apr-2012	8		X	
	Clair, 2019[88]	X	Moderate	Biomedical risk assessment	Sept-2018	20		X	
	Ussher 2019[135]	X	High	Exercise	May-2019	24		X	
	Klinsophon, 2017[102]		Moderate	Exercise	Nov-2016	19		X	
	White, 2014[137‡]	X	High	Acupuncture	Oct-2013	38		X	
	Barnes, 2019 [82]	X	High	Hypnotherapy	July-2018	14		X	X
	Boyle, 2014[84]	X	High	Electronic health records support	July-2014	16		X	
	Thomas, 2017[130]	X	High	System change interventions	Feb-2016	7		X	
Benefits and harms of reduction-to-quit interventions (1 review)	Lindson, 2019c[105]	X	High	Reduce-to-quit interventions	Oct-2018	51		X	X
Benefits and harms of relapse prevention interventions (1 review)	Livingstone-Banks, 2019a[108]	X	Moderate	Relapse prevention	Feb-2018	77		X	
Benefits and harms of behavioral interventions in pregnant persons (5 reviews)	Chamberlain, 2017[185]	X	High	Any behavioral support among pregnant persons	Nov-2015	102	X	X	X
	Griffiths, 2018[186]		Moderate	Digital interventions among pregnant persons	May-2017	12		X	
	Livingstone-Banks, 2019a[108]	X	Moderate	Relapse prevention among pregnant persons	Feb-2018	77		X	
	Notley, 2019[116]		High	Incentives among pregnant persons	July-2018	10		X	X
	Wilson, 2018[187]		Moderate	Psychotherapy or incentive-based interventions	July-2017	22		X	

Table 2. Characteristics of Included Systematic Reviews by Review Focus, Intervention, and Last Search Date

Focus (Number of reviews)	Author, Year	Primary review*	Quality†	Specific intervention or subgroup	Last search date	Total # of included studies	KQ 1: Health outcomes	KQ 2: Cessation	KQ 3: Harms
Reviews limited to other subgroups (21 reviews)	Wu, 2015[141]		Moderate	Subgroup: Adults not motivated to quit Any tobacco cessation intervention	Apr-2015	14		X	X
	Appolonio, 2016[81]		High	Subgroup: Adults with alcohol or drug dependence Any tobacco cessation intervention	Aug-2016	34		X	
	Thurgood, 2016[132]		High	Subgroup: Adults with alcohol or drug dependence Any tobacco cessation intervention	Aug-2014	17		X	
	Wilson, 2017[139]		Moderate	Subgroup: Disadvantaged persons Any behavioral support	Jan-2017	24		X	
	Boland, 2016[83]		Low	Subgroup: Disadvantaged persons Mobile phone- or internet-based support	May-2016	13		X	
	Liu, 2013[107‡]		Low	Subgroup: Ethnic minorities Adapted interventions for ethnic minorities	Apr-2013	28		X	
Subgroups continued	Johnston, 2013[99‡]		Low	Subgroup: Ethnic minorities Any tobacco cessation intervention	May-2012	5		X	
	Carson, 2012[86‡]		High	Subgroup: Ethnic minorities Any tobacco cessation intervention	April-2011	4		X	X
	Schuit, 2017[122]		High	Subgroup: Genetic biomarker differences NRT, bupropion, varenicline	Aug-2016	18		X	
	Khanna, 2016[100]		High	Subgroup: Persons with SMI Advice	Apr-2015	0		X	
	Tsoi, 2013[133‡]		High	Subgroup: Persons with SMI Any tobacco cessation intervention	Oct-2012	34		X	X
	van der Meer, 2013[136‡]		Moderate	Subgroup: Persons with SMI Any tobacco cessation intervention	Apr-2013	49		X	
	Peckham, 2017[118]		Moderate	Subgroup: Persons with SMI Any tobacco cessation intervention	Sept-2016	26		X	X
	Roberts, 2016[120]		Moderate	Subgroup: Persons with SMI NRT, bupropion, varenicline	Dec-2014	14		X	X
	Ahmed, 2018[80]		Moderate	Subgroup: Persons with SMI Varenicline	July-2018	4		X	X
	Kishi, 2015[101]		Moderate	Subgroup: Persons with SMI Varenicline (Harms only)	Aug-2014	7			X
	Wu, 2016[142]		High	Subgroup: Persons with SMI Varenicline (Harms only)	Sept-2015	8			X
	Smith, 2016[124]		Low	Subgroup: Sex differences NRT, bupropion, varenicline	Dec-2015	28		X	

Table 2. Characteristics of Included Systematic Reviews by Review Focus, Intervention, and Last Search Date

Focus (Number of reviews)	Author, Year	Primary review*	Quality†	Specific intervention or subgroup	Last search date	Total # of included studies	KQ 1: Health outcomes	KQ 2: Cessation	KQ 3: Harms
	McKee, 2016[112]		High	Subgroup: Sex differences Varenicline	Dec-2014	16		X	
	Ebbert, 2015[92]		High	Subgroup: Smokeless tobacco users Any tobacco cessation intervention	June-2015	34		X	X
	Schwartz, 2016[123]		Low	Subgroup: Smokeless tobacco users Varenicline	Feb-2014	3		X	X

* Primary reviews are those that represented the most current and/or applicable evidence within each population and intervention subgroup and served as the basis for the main findings of this report.
† Review credibility assessed using AMSTAR-2[73]
‡ Included in previous USPSTF review and has not been updated

Abbreviations: KQ = key question; NRT = Nicotine replacement therapy; SMI = severe mental illness

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Stead, 2016[127]	Jul-2015	Adult smokers, excluding pregnant persons	Combined pharmacotherapy and behavioral support	Combined pharmacotherapy and behavioral support	Usual care; brief advice	Smoking abstinence	Any	≥6 months	RCTs or quasi-RCT
Hartmann-Boyce, 2018[96]	Jul-2017	Smokers of any age motivated to quit	NRT	NRT	Placebo; non-NRT control	Smoking abstinence; AEs; SAEs	NR	≥6 months	RCTs or quasi-RCTs
Lindson, 2019a[104]	Apr-2018	Smokers of any age motivated to quit	NRT, different doses, durations, and combinations	Any form, dose, duration, schedule of NRT use	Any other forms, doses, durations, or schedules of NRT	Smoking abstinence; AEs; SAEs; drop-outs due to AEs	Any	≥6 months	RCTs
Howes, 2020[98, 211]	Apr-2019	Smokers of any age, excluding pregnant persons	Bupropion	Antidepressant medication, including bupropion	Placebo; no pharmacotherapy; alternative therapeutic control; different dosage of antidepressant	Smoking abstinence; AEs; SAEs; drop-outs due to AEs	NR	≥6 months	RCTs
Cahill, 2016[85]	May-2015	Adult smokers, excluding smokeless tobacco users	Varenicline	Selective nicotine receptor partial agonists, including varenicline	Placebo or alternative pharm	Smoking abstinence; AEs; Cardiovascular AEs; SAEs	NR	≥6 months	RCTs
Chang, 2015[87]	Nov-2014	Adult smokers	Varenicline + NRT	Combination treatment of varenicline and NRT	Varenicline	Smoking abstinence; AEs	NR	NR	RCTs
Hollands, 2019[97]	Sept-2018	Adult smokers	Support for medication adherence	Intervention with clear focus on increasing adherence to pharmacotherapy for tobacco cessation	Usual care	Smoking abstinence; AEs	NR	≥6 months	RCTs or quasi-RCTs
Mills, 2010[114]	Nov-2009	Smokers of any age	NRT (Harms only)	Any form of NRT (lozenge, skin patch, gum, nasal spray, inhaler, and tablet)	Placebo or standard of care	AEs	Any	Any	RCTs and observational studies

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Mills, 2014[113]	Mar-2013	Smokers of any age	NRT, bupropion, varenicline (Harms only)	NRT, bupropion, or varenicline	Placebo or no drug	Cardiovascular AEs	NR	Any	RCTs
Thomas, 2015[131]	May-2014	Any*	Varenicline (Harms only)	Varenicline at the maximum dosage (1 mg twice daily)	Placebo	AEs; Psychiatric AEs	Any	Any followup accepted	RCTs
Sterling, 2016[128]	Jun-2015	Tobacco users of any age	Varenicline (Harms only)	Varenicline	Placebo; behavioral intervention applied equally in intervention and control groups	Cardiovascular AEs; SAEs	NR	During study treatment or within 30 days of drug discontinuation	RCTs
Hartmann-Boyce, 2019[95]	June-2018	Smokers of any age, excluding pregnant persons	Behavioral support as an adjunct to pharmacotherapy	Behavioral support as an adjunct to pharmacotherapy, where all participants had access to a smoking cessation pharmacotherapy and in which one or more intervention conditions received more intensive behavioral support than the control condition	Any behavioral support of a lower intensity than the intervention or testing specific behavioral components but matched for contact frequency and duration	Smoking abstinence	Any	≥6 months	RCTs or quasi-RCTs
Stead, 2013[125]	Jan-2013	Smokers of any age, excluding pregnant persons	Physician advice	Physician advice to stop smoking. Advice was defined as verbal instructions from the physician with a "stop smoking" message irrespective of whether or not information was provided about the	No advice; usual care; differing levels of physician advice	Smoking abstinence	Any	≥6 months	RCTs or quasi-RCTs

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
				harmful effects of smoking					
Rice, 2017[119]	Jan-2017	Adult smokers, excluding pregnant persons	Nurse support	Nursing intervention, defined as the provision of advice, counseling, and/or strategies to help people quit smoking. Advice was defined as verbal instructions from the nurse to stop smoking, whether they provided information about the harmful effects of smoking	Usual care; brief advice; no intervention	Smoking abstinence	Any	≥6 months	RCTs
Lancaster, 2017[103]	May-2016	Adult smokers, excluding pregnant persons	Individual behavioral counseling	Individual counseling consisting of a face-to-face encounter between a smoker and a counselor trained in assisting smoking cessation, including counseling as an addition to pharmacotherapy†	NR	Smoking abstinence	NR	≥6 months	RCTs or quasi-RCTs
Stead, 2017[126]	May-2016	Adult smokers, excluding pregnant persons	Group behavioral therapy	Group behavioral therapy in which smokers met for scheduled meetings and received some form of behavioral intervention, such as information, advice and encouragement or cognitive behavioral therapy delivered over at least two sessions	Non-group-based cessation intervention; no-intervention control	Smoking abstinence	Any, except for antenatal care settings	≥6 months	RCTs

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Lindson, 2019b[106]	Aug-2018	Smokers of any age, excluding pregnant persons	Motivational interviewing	Behavioral intervention using motivational interviewing	No intervention, another smoking cessation intervention of any length or intensity, another type of MI intervention	Smoking abstinence	NR	≥6 months	RCTs
Moyo, 2018[115]	July-2017	Adult smokers	Decision aids	Any tool a healthcare provider used to share with and inform people about treatment options, including print, video, and computer-based aids	Usual care without the use of shared decision-making and decision aids	Smoking abstinence	Any	Any	RCTs, nonrandomized controlled trials, before and after studies, interrupted time-series
Livingstone-Banks, 2019b[109]	Mar-2018	Adult smokers, excluding pregnant persons	Print-based interventions	Print-based self-help intervention, defined as any manual or program designed to be used by individuals to assist a quit attempt that is not aided by health professions, counselors, or group support	Another print-based self-help intervention; minimal control.	Smoking abstinence	NR	≥6 months	RCTs or quasi-RCTs
Matkin, 2019[110]	May-2018	Smokers of any age	Telephone counseling	Telephone counselling alone, in combination with self-help materials, or as an adjunct to another smoking cessation treatment	Minimal intervention; brief intervention; no telephone counselling	Smoking abstinence	NR	≥6 months	RCTs or quasi-RCTs
Whittaker, 2019[138]	Oct-2018	Smokers of any age	Mobile phone-based support	Any intervention that could be considered predominantly a mobile phone-based program (such as	NR	Smoking abstinence	NR	≥6 months	RCTs or quasi-RCT

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
				text messaging or smartphone apps) for smoking cessation					
Tzelepis, 2019[134]	Aug-2019	Smokers of any age	Real-time video counselling	Interventions where real-time video counselling was delivered by smoking cessation advisors or healthcare professionals as either the primary intervention or an adjunct to other smoking cessation treatments. Studies were eligible where administration of the intervention occurred via telemedicine video conferencing technology or other platforms such as Skype, FaceTime, Google+Hangouts, Talky Core, Facebook Messenger, Viber, Tango (or both) or alternative forms of video communication.	No intervention control; health information or brief advice; written self-help materials; proactive telephone counselling; individual face-to-face support; group face-to-face support; web-based interventions or any other smoking cessation intervention	Smoking abstinence	NR	≥6 months	RCTs

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Taylor, 2017[129]	Aug-2016	Smokers of any age, including pregnant women	Internet-based interventions	Internet-based interventions delivered alone or alongside an additional behavioral component or pharmacotherapy	No treatment; other forms of treatment	Smoking abstinence; AEs	Any	≥6 months	RCTs or quasi-RCTs
Notley, 2019[116]	July-2018	Adult smokers	Incentives	Incentive schemes, lotteries, raffles, and contingent or non-contingent payments, to reward cessation and abstinence in smoking cessation programs	Usual care, other smoking cessation intervention without incentives, another incentive-based intervention differing by incentive type or amount	Smoking abstinence, Aes	Any	≥6 months	RCTs
Clair, 2019[88]	Sept-2018	Smokers of any age	Biomedical risk assessment	Biomedical risk assessment in which a physical measurement, such as exhaled carbon monoxide, spirometry, atherosclerotic plaque imaging, or genetic testing was used to increase smoking cessation	Any control group that did not include reporting of such measurements.	Smoking abstinence	NR	≥6 months	RCTs
Ussher, 2019[135]	May-2019	Tobacco smokers wishing to quit, or recent quitters	Exercise	Interventions aimed at increasing exercise, either alone or as an adjunct to a smoking cessation intervention	Smoking cessation program alone or another type of nonexercise control group	Smoking abstinence	NR	≥6 months	RCTs

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
White, 2014[137]	Oct-2013	Tobacco users of any age wishing to stop smoking, excluding pregnant persons	Acupuncture	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)	Smoking abstinence	Any	≥6 months	RCTs
Barnes, 2019[82]	July-2018	Smokers of any age wishing to stop smoking	Hypnotherapy	Hypnotherapy for smoking cessation	No treatment or other therapeutic intervention	Smoking abstinence, Aes	NR	≥6 months	RCTs
Boyle, 2014[84]	Jul-2014	Smokers of any age	Electronic health records support	Interventions that involved electronic health record systems in healthcare settings that were intended to improve documentation or assistance for patients who use tobacco, either by directly prompting clinician, clinic, or health system action or by measuring and reporting on clinical performance	NR	Smoking abstinence; changes in support action (system level)	Healthcare settings	≥6 months	RCTs or observational studies

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Thomas, 2017[130]	Feb-2016	Smokers of any age who are receiving care in a healthcare setting	System change interventions	Policies and practices designed by organizations to integrate the identification of all smokers and the subsequent offering of evidence-based smoking cessation treatments (pharmacological, behavioral, or both) into the routine delivery of health care‡	NR	Smoking abstinence	Any healthcare setting	≥6 months	RCTs or quasi-RCTs
Lindson, 2019c[105]	Oct-2018	Smokers of any age, excluding pregnant persons	Reduction-to-quit interventions	Instruction, advice, or support for participants to reduce the number of cigarettes with an ultimate goal of quitting	No intervention; abrupt quitting interventions, or another reduction-to-quit intervention	Smoking abstinence, Aes	NR	≥6 months	RCTs
Livingstone-Banks, 2019a[108]	Feb-2018	Smokers of any age who quit on their own, were undergoing enforced abstinence, or were participating in treatment programs	Relapse prevention	Any pharmacologic, behavioral, or combination intervention aimed at tobacco relapse prevention	No intervention; shorter intervention; intervention not oriented towards relapse prevention	Smoking abstinence	NR	≥6 months	RCTs or quasi-RCTs

Table 3. Inclusion Criteria of Primary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Last search date	Population	Specific intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Chamberlain, 2017[185]	Nov-2015	Women who are currently smoking or have recently quit smoking and are pregnant; women who are currently smoking or have recently quit smoking and are seeking a pre-pregnancy consultation; health professionals in trials of implementation strategies of psychosocial interventions to support pregnant women to stop smoking.	Any behavioral support	Psychosocial interventions where a primary aim of the study was smoking cessation in pregnancy. Psychosocial interventions were defined as non-pharmacological strategies that use cognitive behavioral, motivational and supportive therapies to help women to quit, including counselling, health education, feedback, financial incentives, social support from peers and/or partners, and exercise interventions, as well as dissemination trials	Usual care; less intensive intervention; alternative intervention	Smoking abstinence; Aes; smoking reduction; relapse prevention; perinatal outcomes; maternal outcomes; healthcare utilization	Any	≥6 months, ≥12 months (postpartum); late pregnancy	RCTs or quasi-RCTs

* Includes studies among smokers and non-smokers

† Excludes studies of counseling delivered by doctors or nurses and studies of motivational interviewing as those studies are captured in other reviews

‡ Interventions that include at least one of the following six system-level strategies: 1. Implement a system for identifying smokers and documenting tobacco-use status in every clinic and hospital; 2. Provide education, resources and feedback to promote provider interventions; 3. Dedicate staff to provide smoking cessation treatment and assess its delivery in staff performance evaluations; 4. Promote hospital policies that support and provide smoking cessation services; 5. Provide evidence-based tobacco dependence treatments (both counselling and pharmacotherapy); 6. Reimburse providers for the delivery of effective tobacco dependence treatments and include these services among their defined duties.

Abbreviations: AE = Adverse event; mg = milligram; MI = motivational interviewing; NR = Not reported; NRT = Nicotine replacement therapy; RCT = Randomized controlled trial; SAE = Serious adverse event

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
Stead, 2016[127]	Combined pharmacotherapy and behavioral support	53	15 – 5887	31 – 65	11 – 31	Typical intervention involved multiple contacts with a specialist cessation adviser or counsellor, with most participants using some pharmacotherapy and receiving multiple contacts. However, there was a great deal of variation, including some interventions which involved making pharmacotherapy and behavioral components available to a large population in which take-up of treatment was low, or providing a brief intervention to all participants and offering stepped care for those willing to set a quit date. One intervention was delivered entirely by mail or prerecorded phone messages, using an expert system for tailoring contact and two by telephone counselling alone. All others included some face-to-face contact but additional sessions was sometimes provided by telephone. More than half the trials (n = 28, 53%) offered between four and eight sessions and a quarter (n = 13) over eight sessions. The modal category for contact time was 91 to 300 minutes (n = 22, 42%), with 17 (32%) offering between 31 and 90 minutes and eight (15%) over 300 minutes. We categorized interventions according to the maximum planned contact unless session duration was not described, so the typical time per participant would have been smaller, even in studies where the take-up of treatment was high.	Healthcare settings (k=43), community-based recruitment (k=8)	Most counselling and support was provided by specialist cessation counsellors or trained trial personnel. In a small subgroup the intervention was largely given by usual care providers including general practitioners/family physicians, dental hygienists, dentists and dental hygienist, or occupational physicians. Two studies used peer group counsellors and one used trained lay adviser.
Hartmann-Boyce, 2018[96]	NRT	136	50 – 8000	15 – 62	8 – 38	Most trials comparing nicotine gum to control provided the 2 mg dose. A few provided 4 mg gum to more highly addicted smokers, and two used only the 4 mg dose. In three trials the physician offered nicotine gum but participants did not necessarily accept or use it. In one trial participants self-selected 2 mg or 4 mg doses. The treatment period was typically two to three months but ranged from three weeks	Primary care practices, workplace clinics (k=2), university clinic (k=1), recruited through community physicians (k=1),	Therapists (sometimes specified as a GP but mostly not specified)

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						to 12 months. Some trials did not specify how long the gum was available. Many of the trials included a variable period of dose tapering, but most encouraged participants to be gum-free by six to 12 months. In nicotine patch trials the usual maximum daily dose was 15 mg for a 16-hour patch, or 21 mg for a 24-hour patch. Thirty-two studies used a 24-hour formulation and nine a 16-hour product; the rest did not specify. One study offered, among other dosage options, a 52.5 mg/24-hour patch. The minimum duration of therapy ranged from three weeks, to three months. There are eight studies of nicotine sublingual tablets or lozenges. Three used 2 mg sublingual tablets. One used a 1 mg nicotine lozenge. One used 2 mg or 4 mg lozenges according to dependence level based on manufacturers' instructions , and one used 2 mg or 4 mg based on participants' time to first cigarette of the day (TTFC); smokers whose TTFC was more than 30 minutes were randomized to 2 mg lozenges or placebo , whilst smokers with a TTFC less than 30 minutes had higher-dose 4 mg lozenges or placebo.	Veterans Affairs Medical Centers, and recruited people with cardiac diseases in the primary care category (k=1), antenatal clinics (k=4), specialized smoking cessation clinics to which participants had usually been referred (k=6), hospital in- or outpatients, some of whom were recruited because they had a co-existing smoking-related illness (k=13), settings intended to resemble 'over the-counter' (OTC) use of NRT (k=3), drug abuse treatment centers (k=2), psychiatric treatment setting (k=1), remaining trials were undertaken in	

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							participants from the community, most of whom had volunteered in response to media advertisements, but who were treated in clinical settings.	
Lindson, 2019a[104]	NRT, different doses, durations, and combinations	63	45 – 3575	15 – 56.7	17 – 38	Trials addressed a range of questions relating to the effectiveness of different types and uses of NRT. The variations on NRT use tested are included in the outcomes.	Community (k=31), internet advertisements (k=1), referrals from clinicians or from healthcare clinics, such as smoking cessation clinics or quitlines, substance abuse clinics, primary care clinics, referrals to a lung health clinic (k=1), previous smoking cessation studies (k=1), worksites (k=2), universities (k=1), a number of studies used a mixture of these approaches	Smoking cessation counsellors, research nurses, physicians

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Howes, 2020[98]	Bupropion (and other anti-depressant)	115	5-8144	16 – 57	5 – 48	Details of interventions not synthesized. Bupropion vs. control (k=46) Comparing different bupropion doses (k=3) Bupropion as an adjunct to NRT vs. NRT (k=16) Bupropion as an adjunct to varenicline vs. varenicline (k=6) Bupropion vs. NRT (k=10) Bupropion vs. varenicline (k=10 trials) Bupropion vs. nortriptyline (k=3) Bupropion vs. gabapentin (k=1) Nortriptyline (k=10) Fluoxetine (k=7) Paroxetine (k=1) Moclobemide (k=1) Selegiline (k=5) Lazabemide (k=1) EVT302 (k=1) Venlafaxine (k=1) St. John's wort (k=3) SAMe (k=1) Sertraline (k=1)	Community-based health care center, cessation outpatient clinics, community clinics, hospitals, community mental health center, Veterans Medical Center, primary care clinics, university, substance use disorder clinics, continuation high schools, preoperative clinic, prisons, HMO, psychiatric research center, anti-smoking clinics, community pharmacy	NR
Cahill, 2016[85]	Varenicline	44	32 – 8144	38 – 57	NR	33 studies used the standard 12-week regiment of varenicline, routinely titrating the first week up to the recommended daily dose of 1 mg twice a day; 3 trials compared different dosage arms of varenicline against a placebo arm; 1 trial in non-responders regulated dosage up to the target quit date (day 21) to a maximum of 5 mg a day; 1 allowed participants to regulate their own dosage throughout the treatment phase; 5 trials used NRT as a comparator condition	Smoking cessation clinics, hospitals, universities, and other research centers	NR

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						and provided a 12-week course, reducing the dosage as a weaning process; 2 trials provided an 8-week course, one of which progressively reduced the dosage at the end of treatment; 1 trial gave a 24-week course of NRT, tailored to the level of nicotine dependency, and matched to the duration of the placebo and varenicline arms of the trial; 5 trials used Bupropion SR at 150 mg twice a day, 4 for 12 weeks and 1 for 7 weeks.		
Chang, 2015[87]	Varenicline + NRT	3	117 – 435	44.5 – 46.3	NR	One study administered trial patch two weeks before the Target Quit Date (TQD), while the other two studies started patch use on the TQD. Two studies used a 15 mg/16 hours patch, while the other used a 21 mg/24 hours patch. The use of varenicline was similar among the studies: All started at 0.5 mg per day one week before TQD, with increase to 2 g/day on TQD, and continued for 12 weeks. One study tapered the dose of varenicline on the 13th week. All studies provided concurrent behavioral counseling during the treatment phase.	NR	NR
Hollands, 2019[97]	Support for medication adherence	10	40 – 928	32- 49	NR	The interventions typically provided information on the rationale for, and emphasized the importance of, adherence to medication, and aided participants in developing strategies to overcome problems and barriers to maintaining adherence. As such, they included a combination of two intervention strategies: a) instruction for patients on medication use or b) counselling about smoking, and the value of medication in overcoming addiction.	Clinic settings apart from one study delivered by phone	Trained counselors, project staff, nurses, cognitive behavioral therapy practitioners
Mills, 2010[114]	NRT (Harms only)	120	7 – 1,429 (RCTs) 22 – 65,599 (obs)	NR	21 – 35	Details of interventions not synthesized. RCTs (k=92); placebo controlled (k=83): Patch (k=42) Gum (k=26) Spray (k=6)	NR	NR

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						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 observational studies included co-interventions Counseling (k=12) Behavior/behavior modification (k=3) Education (k=3) Self-help booklet (k=1)		
Mills, 2014[113]	NRT, bupropion, varenicline (Harms only)	63	32 – 3,296	NR	17 – 31	Details of interventions not synthesized. NRT vs. placebo (k=19) Bupropion vs. placebo (k=27) Varenicline vs. placebo (k=18) High-dose NRT vs. placebo (k=1) Combination NRT vs. control (k=1) Bupropion vs. varenicline (k=2) Bupropion vs. NRT (k=3) Varenicline vs. NRT (k=1)	NR	NR
Thomas, 2015[131]	Varenicline (Harms only)	44	9 – 1210	15 – 72	Average, 20 (range NR)	Varenicline at the maximum dose (1 mg twice daily)	Smokers in hospital (k=1)	NR
Sterling, 2016[128]	Varenicline (Harms only)	38	10 – 1510	13.5 – 69.1	10.7 – 26.0	The most common dose of varenicline was 1 mg twice daily, with some studies in which lower doses were prescribed. Length of	Varied: General population, inpatient,	NR

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						treatment with varenicline ranged from 1 to 52 weeks, with the majority of studies treating patients for 12 weeks.	outpatient	
Hartmann-Boyce 2019[95]	Behavioral support as an adjunct to pharmacotherapy	83	30 – 4614	17 – 61	21.2	NRT was offered in the majority of studies, with 41 providing nicotine patch only. Most provided a supply of NRT for between eight and 12 weeks. Eight studies used nicotine gum only, one used sublingual tablets and three did not specify the type. Five studies offered patch and/or gum. Seven studies provided bupropion alone, one provided nortriptyline alone and four provided varenicline alone. Three studies offered a choice of pharmacotherapy; NRT or bupropion, or NRT, bupropion, or varenicline. Three studies provided combination therapy of both NRT and bupropion. The intensity of the behavioral support, in both the number of sessions and their duration, was very varied for both intervention and control conditions. In seven trials, there was no counselling contact for the controls. In 30 studies, the control arms had between one and three contacts (which could be face-to-face or by telephone) and most of these had a total contact duration of between four and 30 minutes. In 34 studies, the control group was scheduled to receive between four and eight contacts, with all except eight involving a total contact duration of over 90 minutes. Twelve studies offered over eight contacts for the controls. Typically, the intervention involved only a little more contact than the control, so that the most intensive interventions were compared with more intensive control conditions. In five trials, the intervention consisted of between one and three sessions, with a total duration of 31 to 90 minutes. Forty-five studies tested interventions of between four and eight sessions, about half of which were in the 91- to 300-minute-duration category. The	Primary care, chest clinic, cardiovascular disease outpatient clinic, rheumatology clinic, immunology clinic, HIV clinic, lesbian, gay, bisexual, and transgender health center, mental health clinic, mental health research center, substance abuse clinic, Veterans Administration hospital, cardiac ward, any ward	Trained counselors, community-based educators, nurse practitioners, research staff with bachelor's degree or higher, psychologists, masters-level counselors, research nurses, telephone counselors, exercise physiologist, smoking cessation specialists, trained advisors, abuse therapist, physicians, American Cancer Society-trained volunteers, advisors from helpline centers, wellness coaches, trained facilitator, study personnel,

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						remaining 32 studies offered more than eight sessions, typically providing over 300 minutes of counselling in total.		mental health clinicians
Stead, 2013[125]	Physician advice	42	60 – 3,215	NR	13 – 25	The definition of what constituted 'advice' varied considerably. In one study participants were asked whether they smoked and were given a leaflet if they wanted to stop. The control group were not asked about their smoking status until followup. In all other studies the advice included a verbal 'stop smoking' message. This verbal advice was supplemented by provision of some sort of printed 'stop smoking' material (27 studies), or additional advice from a support health worker or referral to a cessation clinic or both. Four studies described the physician intervention as behavioral counselling with a stop-smoking aim. One study compared motivational consulting (based on information from theoretical models) with simple advice. In two studies the smoker was encouraged to make a signed contract to quit. One study provided an incentive (a telephone card) to those who successfully quit. Three studies included an intervention which involved a demonstration of the participant's pulmonary function), or expired air carbon monoxide. One study, using a cluster design, compared information and a letter alone to advice from a pediatrician to mothers of babies attending well-baby clinics with a view to reducing exposure of the children to passive smoke. One study used a computer-generated tailored report to assist with cessation, and another study compared brief advice to computer-generated tailored letters and to no intervention. One study compared brief advice, tailored letters and the combination of both. It only contributed to the direct comparison of advice and tailored letters.	Mostly family/general practice, but also government clinic, adult diabetic outpatient clinic, hospital cardiac unit, worksite, and community settings	Health care personnel (e.g., medical registrar, physicians, hospital consultants)

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Rice, 2017[119]	Nurse support	59	25 – 2700	20.3 – 70	12 – 23	Nine studies examined a smoking cessation intervention as a component of multiple risk factor reduction interventions in adults with cardiovascular disease; 36 interventions were considered high-intensity (i.e., initial contact lasted more than 10 minutes, there were additional materials or strategies or both, other than simple leaflets, and usually participants had more than one follow-up contact and 7 were considered low intensity (i.e., advice was provided with or without a leaflet during a single consultation lasting 10 minutes or less, with up to one follow-up visit). Eleven studies compared two different interventions including a nursing intervention, testing additional components or different intensities of the intervention.	Recruited from primary care or outpatient clinics (k=28), hospitalized patients (k=22), remaining trials recruited from workplaces, community-based settings, pediatric clinics, home healthcare, and university.	Nurses or health visitors
Lancaster, 2017[103]	Individual behavioral counseling	49	39 – 2095	24 – 63	8 – 29	Counselling interventions typically included the following components: review of a participant's smoking history and motivation to quit, help in the identification of high-risk situations, and the generation of problem-solving strategies to deal with such situations. Counsellors may also have provided non-specific support and encouragement. Some studies provided additional components such as written materials, video or audiotapes.	Healthcare and community settings; primary care (k=4)	Generally described as smoking cessation counselors; professional backgrounds included social work, psychology, psychiatry, health education and nursing
Stead, 2017[126]	Group behavioral therapy	66	45 – 2720	21 – 61	13 – 32	Most programs used between six and eight sessions, with the first few sessions devoted to discussion of motivation for quitting, health benefits, and strategies for planning a quit attempt. Specific components at this stage may include signing a contract to quit, or making a public declaration, and nicotine fading (changing the type of cigarette smoked to a lower nicotine brand). Participants may	Most studies recruited community volunteers; recruited in primary care settings (k=3); recruited participants with	NR

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						also keep records of the number of cigarettes smoked and the triggers for smoking (self-monitoring). Part of the group process also includes discussion and sharing of experiences and problems (intra-treatment social support). Participants may also be instructed on ways to seek appropriate support from friends, colleagues and family (extra-treatment social support). A range of other problem-solving skills may also be introduced, including identifying high-risk situations for relapse, generating solutions and discussing or rehearsing responses. Some programs incorporate more specific components intended to help manage poor mood or depression associated with quitting and withdrawal.	specific health problem (inpatient included) (k=5); conducted or recruited at work site (k=4)	
Lindson, 2019b[106]	Motivational interviewing	37	56 – 4614	15 – 63	2 – 30	All of the studies included in this review made explicit reference to using MI principles defined by Miller and Rollnick. Most studies merely specified that the intervention was carried out according to established MI techniques, rather than providing a more detailed description of counselling content. MI was conducted in one to 12 sessions, with the total duration of MI ranging from five to 315 minutes across studies. MI was delivered in face-to-face sessions in 17 of the 37 studies; in another 12 studies, the counselling was delivered in a combination of face-to-face and telephone sessions, usually with an initial session or sessions conducted face-to-face, followed by follow-up counselling over the phone. Six studies provided counselling over the phone only; a further study had an MI intervention group that received calls and text messages based on CBT and MI and another MI group that received text messages only, and a final study provided MI counselling for adolescents in an online virtual environment. Twenty of the 37 studies	NR	Physicians, nurses, counselors/psychologists, specialist smoking cessation advisors, and lay healthcare workers

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						offered or recommended the use of pharmacotherapy for smoking cessation to all, or a subset of participants.		
Moyo, 2018[115]	Decision aids	7	8 – 1014	NR	NR	Only two decision aids were delivered directly by a healthcare provider. The other studies all evaluated a decision aid where provider follow-up was optional based on the participant's decision after use of the aid. The decision aids in all of the included studies were used at a single time point and included web- or computer-based aids, videos, print materials, or a combination of aids.	Outpatient clinic, psychosocial rehabilitation centers	NR
Livingstone-Banks, 2019b[109]	Print-based interventions	75	40 – 6697	34 – 57*	15 – 32	Thirty-four of the included studies compared standard self-help materials with no intervention or provided standard materials as an adjunct to advice. The other studies compared targeted or tailored self-help methods or compared other variations of programs. Some studies used multiple interventions, testing the effects of different types of information or of increasing amounts of material. Studies of self-help materials were carried out in a range of settings. Some studies provided the materials without face-to-face contact or any additional motivating strategy. Some studies tested the use of materials for people who had called quitlines (self-help materials were the main form of support offered) or the use of materials as an adjunct to counselling. In healthcare settings, studies more frequently provided self-help materials as an adjunct to brief advice to quit. Some studies described as testing self-help materials included relatively high levels of face-to-face support, although less than informal counselling programs. Most studies did not specify an interest in quitting as a selection criterion. The content and format of the self-help programs varied. The most frequently used materials were the American	Studies of self-help materials were carried out in a range of settings	NR

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						Lung Association (ALA) cessation manual: Freedom from Smoking in 20 days, and the maintenance manual: A Lifetime of Freedom from Smoking. Most other programs were not named or described fully. Materials have tended to become more complex over time and to incorporate more techniques from behavior therapy approaches. Most recent studies have used computerized expert systems to provide tailored materials judged to be relevant to the characteristics of each smoker, using baseline data. We specified that materials should contain a structured program for quitting.		
Matkin, 2019[110]	Telephone counseling	104	40 – 7354	15 – 65+	10.6 – 28	Most of the studies were trials of proactive calls from a counsellor, or from an automated interactive voice response system (IVR). Only five assessed interventions that did not involve a counsellor contacting a participant. Some studies included participants who had called helplines that provide smoking counselling (quitlines). Other studies included people who had not called quitlines, but received calls from counsellors or other healthcare providers. Some studies provided telephone counselling alone, but many others provided telephone counselling along with minimal support such as self-help leaflets, or more active support such as face-to-face counselling, or with stop-smoking medication. The number of calls offered ranged from a single call to 12 calls. Some studies only recruited people trying to stop smoking, while others offered support even to those not actively trying to stop. The number, duration and content of the telephone calls was variable. The potential number of calls ranged from one to 12 and in some studies was flexible. The duration of the calls also varied; 10 to 20 minutes was common, although the initial call might be	Recruited participants in healthcare settings and referred them to services provided by quitlines, involving proactive counselling for those following through referral (k=16)	Most of the studies were trials of proactive calls from a counsellor, or from an automated interactive voice response system (IVR)

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						longer. The call schedule could be spaced over weeks or months. We grouped trials into three broad categories: trials of interventions for smokers who contacted a helpline; trials assessing the effect of providing access to a helpline; and trials that offered support proactively in other settings. There are 10 trials that do not fit into any of these categories, so are considered individually.		
Whittaker, 2019[138]	Mobile phone-based support	26	49-8000	18.2-57	14.5	All studies tested automated text messaging interventions. Eighteen studies used text messaging (SMS) as a central component of the intervention. One study sent text messages containing links to theoretically driven video messages from 'ordinary' role models coping with quitting. Several studies paired text messages with in-person visits or assessments. The text message interventions varied in length from one week to five weeks, six weeks, eight weeks, three months, and six months, or were variable. Eight studies did not state that text messages were tailored to the individual. In other studies using text messages, the degree of individual tailoring varied. One study tailored messages to include first name, quit date, top three reasons for quitting, money saved by quitting, and use of quit-smoking medications. Two studies tailored messages to the stage of readiness to quit. Another study's program could be interacted with by reporting changes in smoking behavior (e.g. a quit attempt, relapse), so that appropriate stage-specific messages could be sent. One study tailored their intervention text messages to contain advice and encouragement tailored to participants' current quit status (preparing to quit, first week of the quit attempt, second week of attempt etc.). Two studies tailored the messages to information collected at baseline about the individual. One study	Community	NR

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						individually tailored messages using 24 items from the iQuit questionnaire and information on smoking status at three and seven weeks. Another study matched participant characteristics to messages by keyword to create an individualized program. One study's participants selected the role model from whom they wished to receive messages. A number of text messaging interventions included interactive components such as the ability to text for more support in the instance of cravings or lapses, an optional Quit Buddy, a Quit support network, polls and quizzes, regular checking in on smoking status, and one study included some degree of choice. Participants received offers of support via a personalized tailored Internet program, a text message program, both programs, a choice of all three, or a minimal control.		
Tzelepis, 2019[134]	Real-time video counselling	2	49-566	47.4-51.12	17.0	Both studies delivered real-time video counselling for smoking cessation individually and not in a group format. In one study, the video counselling intervention consisted of eight sessions, while in the other study the intervention comprised four sessions. The length of the video treatment was eight weeks in both studies. One study used 10- to 30-minute video sessions, while the other study did not report video session duration. One study delivered the real-time video counselling intervention via videoconferencing equipment located at primary care clinics, so participants were required to travel to receive video counselling, while the other study delivered the video counselling intervention via software installed on the participants' own smartphones. One study delivered the video counselling intervention between 2009 and 2011 and the other study between 2016 and 2017. Both studies compared the real-time	Community, healthcare	NR

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						video counselling intervention with a telephone counselling intervention for smoking cessation, and delivered the telephone counselling interventions directly to participants via their own telephones. The intended number and timing of sessions, length of treatment and duration of sessions in the telephone counselling interventions were identical to those of the video counselling interventions delivered in each study. One study based the counselling content for both the video counselling and telephone counselling interventions on a behavioral therapy foundation, guided by Bandura's Social Cognitive Theory and, the other study on a combination of motivational interviewing and CBT. A tobacco treatment specialist and a trained graduate student delivered the counselling in one study, and trained counsellors delivered the counselling in the other. One study provided all participants with nicotine patches. The other study provided information about the cessation medications covered by participants' insurance plan or public assistance program, and study staff assisted income-eligible participants with no insurance coverage to apply for cessation medications from the pharmacy assistance programs of pharmaceutical drug companies.		
Taylor, 2017[129]	Internet-based interventions	77	66 – 12,000	16 – 63	NR	Range of interventions provided, 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, from a bulletin board facility, a multimedia component, tailored and personalized access to very high depth tailored stories and highly personalized message sources. Some trials	Recruited from primary care (k=7); most recruitment was web-based with participants finding the sites through search engines and browsing	NR

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						also included counselling or support from nurses, peer coaches or tobacco treatment specialists. Other trials also incorporated online social networks, such as Facebook, Twitter, and WeChat, and online forums, chat rooms, and support groups. Two interventions were very distinct from the rest. In addition to brief smoking advice, one study used an Internet-based three-dimensional face age progression simulation software package to create a stream of aged images of faces from a standard digital photograph. The resulting aged image was adjusted to compare how the participant aged as a smoker versus as a non-smoker. In one study, the authors used an online version of the approach-avoidance task, where participants used the computer mouse to pull (i.e. approach, leading to an enlarged picture) or push (i.e. avoid, leading to a reduced picture) neutral or smoking-related pictures. We also identified nine trials of lifestyle interventions that included a smoking cessation component. These interventions included content on a range of topics, including diet and healthy eating, physical activity and fitness, alcohol and drug use, sexual behavior, unpleasant sexual experiences, bullying, mental health, patient-provider relationships, and medication management.		
Notley, 2019†[116]	Incentives	33	14 – 6006	19.7 – 55	8 – 26	Approximately half of studies offered cash for abstinence (contingent rewards), or monetary incentives in the form of vouchers. Four studies used entry into a prize drawing alongside a guaranteed reward. Two studies used self-deposited money as the reward incentive and a further four studies used a combination of deposit arms with cash rewards or mixed-rewards arms for abstinence at fixed time points. Seven studies	Community setting, clinics, substance misuse clinics, worksites	NR

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Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
						included more complex payment schedules, especially with a 'reset' option, meaning that a non-abstinent biochemically confirmed outcome at any time point would reset the escalating schedule of reinforcement to a lower level, thus reinforcing continued abstinence.		
Clair, 2019[88]	Biomedical risk assessment	20	64 – 2110	31.7 – 53.0	11.9 – 29.2	One included study tested two interventions: the intervention was feedback about genetic susceptibility combined with CO measurement, which could either be compared to a control group of CO measurement alone, or to a control group without biomarker feedback, thereby testing the combination of the two interventions.) Out of the 21 interventions, five tested feedback on smoking exposure, each measuring the effect of exhaled CO measurements. Five studies tested feedback on smoking-related disease risk; of these, four tested feedback about genetic susceptibility to cancer, and one tested feedback about genetic susceptibility to Crohn's disease. Eleven studies assessed feedback on smoking-related harm: four tested the combination of exhaled CO measurement and spirometry; five tested the effect of spirometry alone, or with the addition of feedback on lung age; two tested the effect of undergoing an ultrasonography of carotid arteries (and femoral arteries for one study) with photographic demonstration of atherosclerotic plaques when present	Community (k=1), smoking cessation clinics (k=2), health promotion army clinic (k=1), mental health clinic (k=1), worksite (k=1), research institutes (k=3)	Physician (k=5) Nurse (k=4) Specific study staff member (k=7) Trained health educator or research counsellor (k=2) Principal investigator with help from trained smoking cessation practitioners (k=1) Web-based (k=1)
Ussher, 2019[135]	Exercise	24	20 - 2318	28 - 59	16.76 - 32	Most of the trials employed supervised, group-based cardiovascular-type exercise supplemented by a home-based exercise program and combined with a multi-session cognitive behavioral smoking cessation program. The comparator in most cases was a multi-session cognitive behavioral smoking	Community, healthcare	NR

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
						cessation program alone.		
White, 2014[137]	Acupuncture	38	18 - 651	NR	NR	All acupuncture studies used a traditional approach to acupuncture in choosing points nominated as specific for smoking cessation. Five studies used facial acupuncture and ten used auricular acupuncture alone. All but three of these used some form of continuous stimulation, either needle or pressure device. Eight studies combined body and auricular acupuncture. Three used continuous stimulation with either indwelling needles or seeds. One study used facial, body, indwelling, and sham auricular acupuncture in different groups. Five studies used acupressure alone, three studies used laser; three studies investigated electrostimulation given over the mastoid bone; and four studies gave electrostimulation to the ear (one also used continuous acupressure stimulation).	NR	NR
Barnes, 2019[82]	Hypnotherapy	14	20 – 360	30 – 40	20 – 24	The studies varied in the method of hypnotic induction used, number of hypnotherapy sessions, and duration of hypnotic treatments. The number of hypnotherapy sessions varied from a single session to up to 8 sessions and the total duration of hypnosis ranged from 30 min to 9 hrs. Seven studies provided hypnotherapy in a group format.	NR	NR
Boyle, 2014[84]	Electronic health records support	16	NA	NA	NR	6 RCTs: In each of these studies treatment conditions tested an electronic health record (EHR) with enhancements intended to facilitate the provider interaction with a smoker patient. One study provided intervention clinics with additional tools within the EHR and clinical staff were reminded to use them. In one, the enhancement was based on information in an existing EHR. Clinical staff (physicians and medical assistants) in the intervention clinics received feedback reports on their use of the existing tools with smoking patients. Sherman 2008	General practice/primary care medical clinics (k=14), dental clinic (k=1), hospital (k=1)	Variable

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
						also provided additional tools for clinical staff in the EHR system with some restrictions on use of the tools by the control clinics. The dental study created text boxes or scripts within the intervention clinic dental record. The scripts served as language the dental providers could use based on patient-specific information obtained during the dental encounter. In the other studies, the intervention clinics were able to link patients through the EHR to a telephone quitline, and the quitline proactively called the patient. Other studies: Of the other ten studies, three used a control condition or comparison clinic. In one study, the comparison clinic was a paper records-based clinic without an electronic health record. Another study used four control clinics, two were based on usual care and two had access to a new electronic health record vital sign screen but were provided no training or support on the use of the screen. One study randomly assigned patients in one clinic to either intervention or usual care based on their family medical record number. The seven additional studies measured outcomes before and after the introduction of an enhancement to an existing electronic health record, without any comparison group. One study was conducted in a family practice clinic and a pulmonary specialty clinic within the same health system. Another study was conducted in a single primary care clinic. One study studied the intervention in a single hospital. Two other studies each involved 3 clinics, and another study studied one large health system with 18 primary care clinics. Two studies involved retrospective cohorts. Followup: There was wide variation in the type and length of follow-up across the studies. For example, one study made		

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
						telephone contact with dental patients a few days after a dental visit to measure intervention effects but no other follow-up was conducted. One study collected follow-up data through a patient survey about two weeks after a medical care visit during an eight month study period. One study collected data during a three-month period, and another study collected 12 month outcome data. One study followed patients to 19 months. Another study provided data one year before and one year after the intervention. One study examined outcomes four months before and after implementation. Another study followed a cohort for eight months. One study included patients with two or more visits during a six-month post intervention period. Another study collected outcome data from electronic records 6 months post intervention.		
Thomas, 2017[130]	System change interventions	7	1980 - 66516	30 - 64	NR	All studies included system-level interventions that involved identifying all smokers, training staff, and providing free evidence-based treatment (i.e., NRT or other pharmacotherapy). Five of the included studies also implemented organizational policies to improve access to cessation interventions (e.g., referrals). All included studies provided clinicians with training ranging from 30 minutes to 20 hours.	Primary care clinics (k=2), dental clinics (k=2), community pharmacy (k=1), VA medical center (k=1), pediatric practice (k=1)	All health professionals including pharmacists and dentists.
Lindson, 2019c[105]	Reduction-to-quit interventions	51	24 - 3297	15.4 – 57.9	11 - 31	Reduction methods varied greatly: some studies simply asked participants to reduce the amount they smokers whereas others provided detailed instructions or suggestions on how to do so, including a goal number of cpd, gradually increasing time between cigarettes, increasing time in the morning before first cigarette, reducing scenario-specific smoking, or replacing cigarette smoking with a form of pharmacotherapy.	Primary care, smoking cessation clinics, worksite, and community	NR

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
Livingstone-Banks, 2019a[108]	Relapse prevention	77	11 - 18010	19 - 60	10.2 - 29.9	Pharm interventions consisted of varenicline, rimonabant, NRT, and bupropion; behavioral interventions consisted of brief interventions (phone calls, mailings, written pamphlets), pharm in conjunction with behavioral support, a 50-minute in person training session, self-help materials, support groups, and group training sessions.	Cessation clinic, participants' own homes, Quitline, community, hospital, mobile applications, Naval training, hospitals, HMO health center, community mental health centers, antenatal clinics, maternity services, mail, Air Force, substance abuse outpatient facility, prenatal clinic, workplaces, Army Medical Center, Quit for Life employers/health plans, obstetric clinics, pediatric practices, narcotics treatment centers	NR
Chamberlain, 2017[185]	Any behavioral support	102	24 - 15,530	19.4 - 30.8	6 - 18	Interventions: Smoking cessation interventions implemented during pregnancy differ substantially in their intensity, their duration, and the people involved in their implementation. In 57/106 study arms the	Most trials of interventions to support pregnant women were conducted in	In 27 study arms the intervention was provided by staff involved in routine

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
						intervention was coded as a single intervention, therefore the 'main intervention strategy' most accurately reflects the type of intervention. However, in 36 study arms the intervention was coded as 'multiple', where other components of the intervention were offered to all women. In 12 studies the intervention was coded as 'tailored' whereby different intervention components were offered and tailored to women's needs. Of the 56 study arms coded as counselling, most involved face-to-face contact, using a variety of strategies either alone or in combination (such as motivational interviewing, cognitive behavioral therapy, stages of change). Four trials with the main intervention strategy coded as counselling included a lottery chance for women who reported quitting; nine included support from peers and/or partners with three of these including support for partners to quit. The duration and frequency of the intervention also varied considerably and has generally increased over time. Twenty of the interventions involved telephone counselling and in five of these studies all counselling was provided via telephone, and one had only brief additional face-to-face contact. Thirty-eight study arms included self-help manuals as part of the intervention, and in 27 study arms there was a brief introduction to the manuals (less than five minutes) and the intervention was therefore coded as counselling, with sensitivity analysis conducted to assess the independent effect of these studies. In 10 study arms the intervention involved use of a video; 11 study arms included use of computers in the intervention. Studies using tools or technology where there was no clear personal contact were coded as health education, including: self-help manuals; text	public hospitals or community antenatal clinics	pregnancy care (coded as effectiveness studies), and in 70 study arms the intervention was provided by dedicated research project staff (coded as efficacy studies), with 11 coded as unclear or not applicable as dissemination trials or the intervention was automated (e.g. text messaging) or provided by use of other materials (e.g. mail-outs).

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
						messaging; audiotape; and computer. Three other studies that reported the intervention consisted of advice to quit only, either in person or by post were coded as health education. Among all 120 study arms with and without outcomes: six dissemination trials were identified, carried out in Australia, the US, and Europe. Three trials reported only dissemination outcomes, and not the primary outcomes of abstinence in late pregnancy, therefore outcomes not able to be included in the meta-analysis are reported in Table 1. Nine studies (with 12 study arms) were cluster-randomized at service level, providing an indication of implementation under routine care conditions; while four studies were cluster-randomized at provider level. Comparisons: Women in the control arms in 56 of 106 study arms with primary outcome data received 'usual care' in relation to smoking cessation, which generally included information about the risks of smoking and advice to quit. In 44 study arms the comparison group received some kind of 'less intensive' intervention, which included studies where a dedicated research team consistently provided what they considered to be 'usual care' for women in the comparison group. In six study arms the comparison group received an 'alternative intervention', which was categorized as having the same intensity (duration and frequency) as the intervention group, providing a comparison as close to a 'placebo-controlled trial as is feasible for psychosocial interventions, to assess the independent effect of the intervention component). One was a counselling intervention using cognitive behavioral therapy compared with traditional health		

Table 4. Descriptive Characteristics of Included Studies Within the Primary Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions, by Intervention Type

Author, Year	Specific intervention	Number of included studies	Sample size (Range)	Mean age (Range)	Mean CPD at BL (Range)	Intervention description	Setting	Providers
						education, one compared two types of text messaging strategies, and four compared provision of incentives, contingent or not contingent on smoking status. As expected, the intensity of both interventions and controls has increased over time, as indicated by the change in frequency and duration of contact during the interventions. In many cases the comparison/control group was described as receiving 'usual care' without specifying further what constituted usual practice (at a particular time and in a particular setting) with respect to advice and assistance.		

*****1 trial ~47% mean age <30; 1 trial ~62% fell between ages 20-39; 1 trial ~44% were >50
†Evidence for general (non-pregnant) adults only

Abbreviations: BL = Baseline; CBT = Cognitive behavioral therapy; CO = Carbon monoxide; CPD = Cigarettes per day; GP = General practitioner; HIV = Human immunodeficiency virus; HMO = Health maintenance organization; mg = milligram; MI = Motivational interviewing; NR = Not reported; NRT = Nicotine replacement therapy; RCT = Randomized controlled trial; SAMe = S-adenosyl-L-methionine; SMS = Short message service; TTFC = Time to first cigarette of the day; WIC = Women, infants, and children

Table 5. Smoking Cessation* Results at 6 or More Months† (KQ 2) From Reviews of Tobacco Cessation Interventions Among Adults, by Type of Intervention

Author, Year	IG	CG	# of RCTs	N analyzed	IG events	IG N	IG quit rate‡	CG events	CG N	CG quit rate‡	Risk ratio (95% CI)	I^2
Stead, 2016[127]	Combined pharmacotherapy and behavioral support	Brief advice or usual care	52	19,488	1529	10,070	15.2%	808	9418	8.6%	1.83 (1.68, 1.98)	36%
Hartmann-Boyce, 2018[96]	NRT, any form	Placebo or no drug	133	64,640	5574	32,918	16.9%	3315	31,722	10.5%	1.55 (1.49, 1.61)	39%
	NRT, gum	Placebo or no drug	56	22,581	1732	10,596	16.3%	1196	11,985	10.0%	1.49 (1.40, 1.60)	40%
	NRT, patch	Placebo or no drug	51	25,754	2160	13,773	15.7%	1131	11,981	9.4%	1.64 (1.53, 1.75)	24%
	NRT, inhaler	Placebo or no drug	4	976	84	490	17.1%	44	486	9.1%	1.90 (1.36, 2.67)	0%
	NRT, intranasal spray	Placebo or no drug	4	887	107	448	23.9%	52	439	11.8%	2.02 (1.49, 2.73)	0%
	NRT, tablets	Placebo or no drug	8	4439	488	2326	20.9%	273	2113	12.9%	1.52 (1.32, 1.74)	71%
	NRT, participant's choice	Placebo or no drug	7	8288	793	4179	19.0%	569	4109	13.8%	1.37 (1.25, 1.52)	42%
Lindson, 2019a[104]	NRT combination	NRT single form	14	11,356	881	5218	16.9%	852	6138	13.9%	1.25 (1.15, 1.36)	4%
Howes, 2020[98]	Bupropion	Placebo or no drug	46	17,866	1846	9714	19.0%	900	8152	11.0%	1.64 (1.52, 1.77)	15%
Cahill, 2016[85]	Varenicline	Placebo	27	12,625	1695	6632	25.6%	668	5993	11.1%	2.24 (2.06, 2.43)	60%
Hughes, 2014[211]	Nortriptyline	Placebo	6	975	96	480	20.0%	49	495	9.9%	2.03 (1.48, 2.78)	16%
Howes, 2020[98]	Bupropion	NRT, any form	10	9230	681	3563	19.1%	987	4667	21.1%	0.99 (0.91, 1.09)	18%
Howes, 2020[98]	Bupropion	Varenicline	6	6286	474	3096	15.3%	677	3190	21.2%	0.71 (0.64, 0.79)	0%
Cahill, 2016[85]	Varenicline	NRT, any form	8	6264	767	3227	23.8%	575	3037	18.9%	1.25 (1.14, 1.37)	39%
Hollands, 2019[97]	Support for medication adherence	Usual care	5	3593	412	1816	22.7%	361	1777	20.3%	1.16 (0.96, 1.40)	48%
Hartmann-Boyce 2019[95]	Behavioral therapy as an adjunct to pharmacotherapy	Pharmacotherapy	65	23,331	2291	11,630	19.5%	2006	11,701	17.1%	1.15 (1.08, 1.22)	8%
Stead, 2013[125]	Physician advice	Usual care	26	22,239	1008	12,583	8.0%	462	9656	4.8%	1.76 (1.58, 1.96)	40%

Table 5. Smoking Cessation* Results at 6 or More Months† (KQ 2) From Reviews of Tobacco Cessation Interventions Among Adults, by Type of Intervention

Author, Year	IG	CG	# of RCTs	N analyzed	IG events	IG N	IG quit rate‡	CG events	CG N	CG quit rate‡	Risk ratio (95% CI)	I^2
Rice, 2017[119]	Nurse advice	Usual care	44	20,881	1607	11,319	14.2%	1165	9562	12.2%	1.29 (1.21, 1.38)	50%
Lancaster, 2017 [103]	Individual counselling with cessation specialist	Minimal contact control	33	13,762	765	6715	11.4%	546	7047	7.7%	1.48 (1.34, 1.64)	46%
Stead, 2017[126]	Group behavioral intervention	Self-help program	13	4395	249	2388	10.4%	116	2007	5.8%	1.88 (1.52, 2.33)	0%
Lindson, 2019b[106]	Motivational interviewing + another smoking cessation intervention	Smoking cessation intervention alone	12	4167	399	2134	18.7%	306	2033	15.1%	1.07 (0.85, 1.36)	47%
Moyo, 2018[115]	Decision aid	Usual care without decision aid	7§	1772	NA	NA	NA	NA	NA	NA	NA‖	NA
Livingstone-Banks, 2019b [109]	Print-based, non-tailored self-help materials¶	No self-help	32	28,451	983	11,114	8.8%	794	13,337	6.0%	1.06 (0.95. 1.19)	25%
	Print-based, non-tailored self-help materials with no face-to-face contact	No self-help	11	13,241	416	6723	6.2%	331	6518	5.1%	1.19 (1.03, 1.37)	0%
	Print-based, tailored self-help materials¶	No self-help	10	14,359	501	6786	7.4%	455	7573	6.1%	1.34 (1.19, 1.51)	0%
Matkin, 2019[110]	Proactive telephone counseling (quitline callers)	Control (various)	14	32,484	2123	19,600	10.8%	1004	12,884	7.8%	1.38 (1.19, 1.61)	72%
	Proactive telephone counseling (not initiated by quitline)	Control (various)	65	41,233	2924	21,001	13.9%	2229	20,232	11.0%	1.25 (1.15, 1.35)	52%

Table 5. Smoking Cessation* Results at 6 or More Months† (KQ 2) From Reviews of Tobacco Cessation Interventions Among Adults, by Type of Intervention

Author, Year	IG	CG	# of RCTs	N analyzed	IG events	IG N	IG quit rate‡	CG events	CG N	CG quit rate‡	Risk ratio (95% CI)	I^2
Whittaker, 2019[138]	Mobile phone-based interventions	Usual care of minimal intervention	13	14,133	694	7324	9.5%	382	6809	5.6%	1.54 (1.19, 2.00)	71%
	Mobile phone-based interventions	No intervention	4	997	64	497	12.9%	39	500	7.8%	1.59 (1.09, 2.33)	0%
Tzelepis, 2019[134]	Real-time video counselling	Telephone counselling	2	608	30	301	10.0%	22	307	7.2%	2.15 (0.38, 12.04)	66%
Taylor, 2017[129]	Internet (interactive and tailored)	Self-help or usual care	8	6786	516	4020	12.8%	356	2766	12.9%	1.15 (1.01, 1.30)	58%
Notley, 2019[116]	Incentives	Usual care or non-incentive-based intervention	30	20,060	1336	12,800	10.4%	516	7260	7.1%	1.49 (1.28, 1.73)	33%
Clair, 2019[88]	Feedback on smoking exposure	Usual care or minimal intervention	5	2368	183	1199	15.3%	179	1169	15.3%	1.00 (0.83, 1.21)	0%
	Feedback on smoking-related disease risk	Usual care or minimal intervention	5	2064	106	1018	10.4%	136	1046	13.0%	0.80 (0.63, 1.01)	0%
	Feedback on smoking-related harms	Usual care or minimal intervention	11	3314	239	1646	14.5%	195	1668	11.7%	1.26 (0.99, 1.61)	34%
Ussher, 2019[135]	Exercise	No exercise	21	6607	457	3326	13.7%	407	3281	12.4%	1.08 (0.96, 1.22)	0%
White, 2014[137]	Acupuncture	Sham acupuncture	9	1892	122	997	12.2%	97	895	10.8%	1.10 (0.86, 1.40)	23%
Barnes, 2019[82]	Hypnotherapy	No intervention or other cessation intervention	14	1926	NA	NA	NA	NA	NA	NA	NA#**	NA
Boyle, 2014[84]	EHR-facilitated interventions	No change to EHR	16††	NA‡‡	NA	NA	NA	NA	NA	NA	NA††	NA
Thomas, 2017[130]	System change interventions	No system changes	7	NA§§	NA	NA	NA	NA	NA	NA	NA‡‡	NA
Lindson, 2019c[105]	Reduction-to-quit interventions	No cessation intervention	6	1599	87	915	9.5%	25	684	3.7%	1.74 (0.90, 3.38)	45%
	Reduction-to-quit interventions	Abrupt quitting interventions	22	9219	584	4922	11.9%	528	4297	12.3%	1.01 (0.87, 1.17)	29%

*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).

†Each review pooled data from the longest followup time point reported at 6 or more months followup

Table 5. Smoking Cessation* Results at 6 or More Months† (KQ 2) From Reviews of Tobacco Cessation Interventions Among Adults, by Type of Intervention

‡Weighted average quit rates
§ Includes 3 RCTs and 4 quasi-experimental studies
‖ No meta-analysis performed. Six studies reported the effects of the intervention on smoking cessation. Only one study reported a statistically significant benefit of the use of a decision aid versus usual care on smoking cessation at 6 months.
¶ Irrespective of level of contact and support common to control group # No overall meta-analysis performed given variation in intensity of the hypnotherapy tested, little information on the hypnotherapy used, and large variation in control conditions
** 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. In the group with the most trials, there was no overall difference in smoking cessation rates between groups at 6 months or greater followup between hypnotherapy versus attention-matched smoking cessation behavioral intervention (RR 1.21 [95% CI, 0.91 to 1.61]; k=6; n=957; I^2=36%)
††Includes 7 RCTs and 9 non-randomized observational studies
‡‡ Only one RCT (n=9589) reported effects on smoking cessation, as captured in the EHR, and found that more intervention vs. control clinic smokers quit (5.3% vs. 1.9%, p<0.001). The remaining studies focused on the impact of EHR changes on smoking support actions by clinicians, clinics, and health systems with most studies reporting improved processes following EHR-facilitated intervention implementation.
§§ Four trials (n=7142) reported the effects of the intervention on smoking cessation finding mixed results. Across all 7 trials, there was mixed evidence on secondary process outcomes such as documentation of smoking status and provision of counseling.

Abbreviations: CG = control group; CI = confidence interval; EHR = electronic health record; I^2 = percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error; IG = intervention group; N = number; RCT = randomized controlled trial; RR = risk ratio

Table 6. Study and Population Characteristics for Evidence on the Use of Electronic Cigarettes for Tobacco Cessation, Sorted by KQ

Key questions	Author, Year Trial name Quality	Country	N rand	Brief population description	Intervention/ Exposure	Comparison	Outcomes of interest
Included for KQ 2 and KQ 3	Bullen, 2013[144] ASCEND Fair	New Zealand	657	Age ≥18 years, had smoked >10 CPD for at least the past year. Wanted to stop smoking	E-cig with 16 mg nicotine/ml plus behavioral support (voluntary quitline) for 13 weeks Device: Elusion e-cigarette with nicotine solution cartridges	CG1: NRT patch (21 mg nicotine per 24 hours) plus behavioral support CG2: E-cig device with placebo (nicotine-free) cartridges plus behavioral support	• Tobacco abstinence at 6 months • Adverse events • Tobacco use outcomes at 6 months
	Caponnetto, 2013[145] ECLAT Fair	Italy	300	Ages 18–70 years, had smoked >10 CPD for at least the past 5 years. Not currently attempting to quit smoking or wishing to do so in the next 30 days	IG1: E-cig with 7.2 mg nicotine cartridges used at will for 12 weeks IG2: E-cig with 7.2 mg nicotine cartridges used at will for 6 weeks and E-cig with 5.4 mg nicotine cartridges for 6 weeks Followed for 1 year (8 visits total) Device: Categoria 401 e-cigarette	Nicotine-free E-cig cartridges	• Tobacco abstinence at 12 months • Adverse events
	Hajek, 2019[154] TEC Fair	UK	886	Adult smokers attending NHS stop-smoking services. No strong preference to use or not to use NRT or e-cigarettes	E-cig starter pack with 30 ml bottle of tobacco-flavored e-liquid with 18 mg nicotine per ml (follow up use of any flavor or strength of e-liquid purchased by participant) for 1 year plus 4 weeks of behavioral support Device: One Kit (Aspire) and One Kit 2016 (Innokin)	NRT (any kind, any combination) plus 4 weeks behavioral support	• Tobacco abstinence at 6 and 12 months* • Adverse events • Tobacco use outcomes at 6 months
	Lee, 2019[157] Fair	Korea	150	Male adults over 18 years, smoked at least 10 CPD during preceding year, had smoked for at least 3 years, and were motivated to quit or reduce cigarette consumption.	E-cig (0.01 mg/mL), distributed in 12-wk supply plus 50-min edu support	Nicotine gum (2mg/tablet), distributed in 12-wk supply plus 50-min edu support	• Tobacco abstinence at 9 to 24 weeks • Adverse events

Table 6. Study and Population Characteristics for Evidence on the Use of Electronic Cigarettes for Tobacco Cessation, Sorted by KQ

Key questions	Author, Year Trial name Quality	Country	N rand	Brief population description	Intervention/ Exposure	Comparison	Outcomes of interest
	Walker, 2019[155] Fair	New Zealand	1124	Ages ≥18 years, current tobacco smokers (any amount) Currently motivated to quit but no use of cessation products in the past year	21 mg, 24-hour nicotine patches + E-cigarette starter kit with a 14 -week supply of 18 mg/mL e-liquid plus 6 weeks of withdrawal-oriented behavioral support Device: eVOD (2nd gen)	CG1: 21 mg, 24-hour nicotine patches + E-cigarette starter kit with a 14 -week supply of no nicotine e-liquid plus 6 weeks of withdrawal-oriented behavioral support CG2: 21 mg, 24-hour nicotine patch for 14 weeks plus 6 weeks of withdrawal-oriented behavioral support	• Tobacco abstinence at 6 and 12 months • Adverse events • Tobacco use outcomes at 6 months
Included for KQ 3 only	Carpenter, 2017[147] Fair	US	68	Age ≥18 years, current smoker of ≥5 CPD for 1 year. At least some concern for health effects of smoking	IG1: E-cig with 16mg nicotine cartridges used at will for 3 weeks IG2: E-cig with 24mg nicotine cartridges used at will for 3 weeks After 3-week sampling period, both groups followed for 3 months (3 follow up visits) Device: BluCig and BluPlus+	No intervention (continued smoking with conventional cigarettes)	• Adverse events • Tobacco abstinence and use outcomes at 4 months (not abstracted)†
	Cravo, 2016[148] Fair	UK	Cohort 1: 408 Cohort 2: 40	Age 21 - 65 years, 5-30 CPD for at least one year. Established smokers not trying to stop smoking or with quit intentions	Cohort 1: E-cig with 2.7 mg nicotine capsules (menthol or tobacco flavor) for 12 weeks Cohort 2: E-cig with 2.7 mg nicotine capsules (menthol or tobacco flavor) with 12 weeks plus 1-week inpatient confinement at onset Device: E-cig Prototype from Fontem Ventures B.V.	Cohort 1: No intervention (continued smoking with conventional cigarettes) Cohort 2: No intervention (continued smoking with conventional cigarettes) plus 1-week inpatient confinement at onset	• Adverse events
	Masiero, 2017[146] Fair	Italy	210	Aged ≥55 years; smoked ≥10 CPD for the past 10 years.	IG1: E-cig with 8mg/mL nicotine concentration - no more than 1 mL of consumption per day – plus behavioral counseling for 3 months	Behavioral counseling	• Adverse events • Tobacco abstinence

Table 6. Study and Population Characteristics for Evidence on the Use of Electronic Cigarettes for Tobacco Cessation, Sorted by KQ

Key questions	Author, Year Trial name Quality	Country	N rand	Brief population description	Intervention/ Exposure	Comparison	Outcomes of interest
				High motivation to stop smoking	IG2: E-cig-like device with nicotine free capsules plus behavioral counseling for 3 months Device: VP5 electronic cigarette		and use outcomes at 3 months (not abstracted)†
	Tseng, 2016[150] Fair	US	99	Age 21–35 years, smoked ≥ 10 CPD. Interested in reducing cigarette consumption	E-cig (disposable, 4.5% nicotine) for 3 weeks plus behavioral counseling to reduce CPD Device: NJOY and King Bold	Placebo E-cig device plus behavioral counseling to reduce CPD	• Adverse events • Tobacco abstinence and use outcomes at 3 weeks (not abstracted)†

*Defined as no more than 5 conventional cigarettes in the 2 weeks after a subject's target quit date.
†Tobacco abstinence outcomes only included for followup ≥6 months

Abbreviations: ASCEND = A Study of Cessation using Electronic Nicotine Devices; CG = control group; CPD = cigarettes per day; ECLAT = EffiCiency and safety of an eLectronic cigAreTte; eCO = expired carbon monoxide; E-cig = electronic cigarette; edu = education; KQ = key question; IG = intervention group; rand = randomized; TEC = Trial of Electronic Cigarettes

Table 7. Smoking Cessation Results at 6 or More Months (KQ 2) for Electronic Cigarettes for Tobacco Cessation, by Author

Author, Year Quality	Population	IG	CG	FU (mo)	IG events	IG N	IG quit rate	CG events	CG N	CG quit rate	Effect estimate (95% CI)	Study product use after abstinence
Bullen, 2013[144, 151] ASCEND Fair	All	E-cig (16mg)	NRT (21mg patch)	6	21	289	7.3%	17	295	5.8%	RR 1.26 (0.68, 2.34)	IG: 38% (8/21) CG: NR
		E-cig (16mg)	Placebo (0mg E-cig)	6	21	289	7.3%	3	73	4.1%	RR 1.77 (0.54, 5.77)	IG: 38% (8/21) CG: NR
	Adults with mental illness	E-cig (16mg)	NRT (21mg patch)	6	2	39	5.1%	5	35	14.%	p=0.245	NR
		E-cig (16mg)	Placebo (0mg E-cig)	6	2	39	5.1%	0	12	NA*	NA*	NR
Caponnetto, 2013[145] ECLAT Fair	All	E-cig (both study groups)[†]	Placebo (0mg E-cig)	12	22	200	11.0%	4	100	4.0%	RR 2.75 (0.97, 7.76), p=0.0561[‡] Adjusted: p=0.04	IG and CG (combined): 26.9% (7/26)
Hajek, 2019[154] TEC Fair	All	E-cig (any)	NRT (any)	6	155	438	35.4%	112	446	25.1%	RR 1.40 (1.14, 1.72) ARR[§] 1.36 (1.15, 1.67)	NR
		E-cig (any)	NRT (any)	12	79	438	18.1%	44	446	9.9%	RR 1.83 (1.30, 2.58) ARR[§] 1.75 (1.24, 2.46)	IG: 80% (63/79) CG: 9% (4/44)
Lee, 2019[157] Fair	All	E-cig	NRT, gum	6	16	75	21.3%	75	21	28.0%	p=0.291	NR
Walker, 2019[155] Fair	All	E-cig (18 mg) + NRT (21mg patch)	Placebo (0mg E-cig) + NRT (21mg patch)	6	35	500	7.0%	20	499	4.0%	RR 1.75 (1.02, 2.98); p=0.038[‖]	Use of both patch and e-cig at 6 months:[#] IG: 11% (36/317) CG: 13% (41/308) Use of e-cig only at 6 months:[#]

Table 7. Smoking Cessation Results at 6 or More Months (KQ 2) for Electronic Cigarettes for Tobacco Cessation, by Author

Author, Year Quality	Population	IG	CG	FU (mo)	IG events	IG N	IG quit rate	CG events	CG N	CG quit rate	Effect estimate (95% CI)	Study product use after abstinence
												IG: 45% (143/317) CG: 36% (111/308)
		E-cig (18 mg) + NRT (21mg patch)	NRT (21mg patch)	6	35	500	7.0%	3	125	2.0%	RR 2.92 (0.91, 9.33); p=0.05‖	Use of e-cig only at 6 months:# IG: 45% (143/317) CG: NR Use of patch only at 6 months:# IG: 22% (70/317) CG: 40% (21/52)

Note(s): Abstinence measured as continuous abstinence and biochemically validated with expired carbon monoxide for all trials.
* Not applicable due to low (0) event rate.
† Group A=7.2 mg E-cig for 12 weeks; Group B=7.2 mg E-cig for 6 weeks and 5.4 mg E-cig for 6 weeks.
‡ Calculated
§Adjusted for trial center, marital status, age at smoking initiation, and score on the Fagerström Test for Cigarette Dependence.
‖ Results based on self-reported quit rate were consistent with 18% of the patch plus nicotine e-cig group versus 11% of the patch plus nicotine-free e-cig group reporting abstinence at 6 months (RR 1.68 [95% CI, 1.22 to 2.30]; p=0.001). Per protocol sensitivity analyses also showed a statistically significant difference (p=0.020).
‖ In contrast, results based on self-reported quit rate showed statistically significantly greater abstinence at 6 months (RR 2.23 [95% CI, 1.19 to 4.15]; p=0.007) among patch plus nicotine e-cig group (18%) versus patches-only group (8%).The per protocol sensitivity analysis did not yield a statistically significant difference (p=0.11).
Adherence was defined as having used the allocated product since last contact. Findings relate to allocated treatment only, in participants for whom adherence data were available. Data does not include adherence in those who crossed-over to an e-cig or those who changed their type of e-cig.

Abbreviations: ARR=adjusted relative risk; CG = control group; eCO=expired carbon monoxide; E-cig = electronic cigarette; IG = intervention group; mg = milligram(s); MI = mental illness; mo = months; NA = not applicable; NR = not reported; NRT = nicotine replacement therapy; RR = relative risk

Table 8. Adverse Event Results (KQ 3) From Systematic Reviews on Pharmacotherapy, by Comparison

Comparison	Author, Year	Adverse event	Subgroup	k	N	IG events	IG N	CG events	CG N	Pooled effect estimate (95% CI)	I2
NRT vs. placebo	Mills, 2010[114]	Mortality	-	8	2765	11	1387	16	1378	OR=0.74 (0.33, 1.67)	0%
		Heart palpitations/ chest pains	-	12	10,234	189	6249	64	3985	OR=2.06 (1.51, 2.82)	0%
	Hartmann-Boyce, 2018[96]	Heart palpitations/ chest pains	-	15	11,074	165	6673	62	4401	OR=1.88 (1.37, 2.57)	10%
	Mills, 2014[113]	CV AEs	-	21	11,647	202	6329	83	5318	RR=1.81 (1.35, 2.43)	0%
		Major CV AEs	-	21	11,647	12	6329	7	5318	RR=1.38 (0.58, 3.26)	0%
NRT: combo vs. single	Lindson, 2019[104]	SAEs	-	6	2888	6	1475	1	1413	RR=4.44 (0.76, 25.85)	35%
NRT, patch: longer duration vs. shorter duration	Lindson, 2019[104]	SAEs	-	3	1173	NR	NR	NR	NR	NA*	NA
NRT, patch: high vs. low dose	Lindson, 2019[104]	SAEs	-	2	1023	7	511	1	512	RR=5.01 (0.87, 28.82)	0%
NRT: combo vs. single	Lindson, 2019[104]	Withdrawals due to treatment	-	7	3070	18	1169	23	1901	RR=1.12 (0.57, 2.20)	73%
NRT, fast-acting vs. NRT, patch	Lindson, 2019[104]	Withdrawals due to treatment	-	4	1482	18	740	4	742	RR=4.23 (1.54, 11.63)	0%
NRT, patch: high vs. low dose	Lindson, 2019[104]	Withdrawals due to treatment	-	2	554	17	277	3	277	RR=4.99 (1.60, 15.50)	0%
NRT, patch: longer duration vs. shorter duration	Lindson, 2019[104]	Withdrawals due to treatment	-	2	648	NR	NR	NR	NR	NA†	NA
Bupropion vs. placebo/no bupropion	Howes, 2020[98]	SAEs	-	21	10,625	139	6094	107	4531	RR=1.16 (0.90, 1.48)	0%
Bupropion vs. placebo	Mills, 2014[113]	CV AEs	-	27	10,402	50	5947	42	4455	RR=1.03 (0.71, 1.50)	0%
		Major CV AEs	-	27	10,402	15	5947	25	4455	RR=0.57 (0.31, 1.04)	0%
	Roberts, 2016[120]	Discontinuation due to AEs	SMI	6	201	6	114	6	87	OR=0.93 (0.18, 4.74)	NR
Bupropion + NRT vs. placebo + NRT	Roberts, 2016[120]	Discontinuation due to AEs	SMI	1	51	2	25	2	26	OR=1.04 (0.14, 8.04)	NR

Table 8. Adverse Event Results (KQ 3) From Systematic Reviews on Pharmacotherapy, by Comparison

Comparison	Author, Year	Adverse event	Subgroup	k	N	IG events	IG N	CG events	CG N	Pooled effect estimate (95% CI)	I2
Varenicline vs. placebo	Cahill, 2016[85]	SAEs	-	29	15,370	269	8125	196	7245	RR=1.25 (1.04, 1.49)	0%
		CV SAEs	-	21	8587	57	4696	35	3891	RR=1.36 (0.91, 2.04)	0%
		Neuropsychiatric SAEs (not deaths)	-	23	8955	41	4920	43	4035	RR=0.82 (0.57, 1.19)	0%
	Mills, 2014[113]	Major CV AEs	-	18	9072	22	5469	13	3603	RR=1.44 (0.73, 2.83)	0%
		CV AEs	-	18	9072	63	5469	41	3603	RR=1.24 (0.85, 1.81)	0%
	Sterling, 2016[128]	Mortality	-	38	12,706	11	7213	9	5493	RR=0.88 (0.50, 1.52)	0%
		CV SAEs	-	38	12,706	57	7213	43	5493	RR=1.03 (0.72, 1.49)	0%
	Thomas, 2015[131]	Suicide and attempted suicide	-	31	9830	4	5352	2	4478	OR=1.67 (0.33, 8.57)	10.3%
		Suicidal ideation	-	20	2990	15	799	18	2191	OR=0.58 (0.28, 1.20)	0%
		Depression events	-	31	9843	163	5356	139	4487	OR=0.96 (0.75, 1.22)	0%
		Mortality	-	36	10,647	13	5760	11	4887	OR=1.05 (0.47, 2.38)	38.7%
	Roberts, 2016[120]	Discontinuation due to AEs	-	5	222	14	131	7	91	OR=1.29 (0.47, 3.56)	NR
	Kishi, 2014[101]	Discontinuation due to all causes	-	7	439	NR	NR	NR	NR	RR=0.92 (0.54, 1.56)	44%
		Discontinuation due to side effects	-	7	439	NR	NR	NR	NR	RR=1.29 (0.67, 2.48)	0%
	Thomas, 2015[131]	Suicidal ideation	Age 40 years and older	18	4782	14	2655	17	2127	OR=0.58 (0.28, 1.24)	0%
Varenicline vs. placebo continued	Thomas, 2015[131]	Depression events	Age 40 years and older	27	9318	144	5050	129	4268	OR=0.99 (0.77, 1.27)	0%
		Suicidal ideation	Age less than 40 years	2	208	1	144	1	64	OR=0.58 (0.28, 1.20)	0%
		Depression events	Age less than 40 years	4	525	19	306	10	219	OR=0.96 (0.75, 1.22)	0%
		Suicidal ideation	50% male	14	3660	12	2097	14	1563	OR=0.57 (0.25, 1.30)	0%

Table 8. Adverse Event Results (KQ 3) From Systematic Reviews on Pharmacotherapy, by Comparison

Comparison	Author, Year	Adverse event	Subgroup	k	N	IG events	IG N	CG events	CG N	Pooled effect estimate (95% CI)	I2
			or greater								
		Depression events	50% male or greater	24	8145	93	4406	89	3739	OR=0.89 (0.66, 1.21)	0%
		Suicidal ideation	Less than 50% male	6	4990	3	702	4	628	OR=0.58 (0.28, 1.20)	0%
		Depression events	Less than 50% male	7	9843	163	5356	139	4487	OR=0.96 (0.75, 1.22)	0%
		Suicidal ideation	50% White or greater	15	3498	11	1956	13	1542	OR=0.56 (0.24, 1.30)	0%
		Depression events	50% White or greater	24	8083	117	4378	95	3705	OR=0.95 (0.72, 1.27)	1.6%
		Suicidal ideation	Less than 50% White	3	681	4	436	2	245	OR=1.83 (0.29, 11.75)	0%
		Depression events	Less than 50% White	4	931	27	562	27	369	OR=0.82 (0.43, 1.58)	0%
		Suicidal ideation	100% with psychiatric illness	5	809	11	416	11	393	OR=0.79 (0.32, 1.93)	0%
		Depression events	100% with psychiatric illness	5	809	31	416	20	393	OR=1.49 (0.84, 2.65)	0%
		Suicidal ideation	10%-20% psychiatric illness	1	192	0	86	1	106	OR=0.16 (0.00, 8.42)	NA
		Depression events	10%-20% psychiatric illness	1	192	6	86	14	106	OR=0.51 (0.20, 1.30)	NA
		Suicidal ideation	No psychiatric illness	14	3989	4	2297	6	1692	OR=0.34 (0.09, 1.29)	0%
Varenicline vs. placebo	Thomas, 2015[131]	Depression events	No psychiatric illness	25	8842	126	4854	105	3988	OR=0.91 (0.69, 1.21)	0%
	Wu, 2016[142]	Suicidal ideation	SMI	4	203	9	124	5	79	RR=1.06 (0.40, 2.82)	0%
		Depressed mood	SMI	3	198	13	121	6	77	RR=1.45 (0.45, 1.64)	28.6%
		Anxiety	SMI	4	267	13	155	14	112	RR=0.77 (0.28, 2.17)	33.7%
	Kishi, 2014[101]	Discontinuation due to side effects	SMI	7	439	NR	NR	NR	NR	RR=1.29 (0.67, 2.48)	0%

Table 8. Adverse Event Results (KQ 3) From Systematic Reviews on Pharmacotherapy, by Comparison

Comparison	Author, Year	Adverse event	Subgroup	k	N	IG events	IG N	CG events	CG N	Pooled effect estimate (95% CI)	I2
		Discontinuation due to all causes	SMI	7	439	NR	NR	NR	NR	RR=0.92 (0.54, 1.56)	44%
	Roberts, 2016[120]	Discontinuation due to AEs	SMI	5	222	14	131	7	91	OR=1.29 (0.47, 3.56)	NR
	Schwartz, 2015[123]	Mood disorders	Smokeless tobacco users	3	744	6	370	9	374	RR=0.71 (0.26, 1.90)	0%

* None of the comparisons based on duration of patch therapy showed a clinically or statistically significant difference for SAEs.
† Not pooled due to substantial heterogeneity; no significant differences in either study

Abbreviations: AE = Adverse event; CG = Control group; CI = Confidence interval; CV = Cardiovascular; IG = Intervention group; NA = Not applicable; NR = Not reported; NRT = Nicotine replacement therapy; OR = Odds ratio; RR = Risk ratio; SAE = Serious adverse event; SMI = Serious mental illness

Table 9. Adverse Event Results (KQ 3) for Primary Evidence on the Use of Electronic Cigarettes for Tobacco Cessation

Author, Year Quality	System or organ class	Outcome	IG	CG	FU (mo)	IG events	IG N	IG AE rate	CG events	CG N	CG AE rate	Effect estimate (95% CI)
Bullen, 2013[144] ASCEND Fair	General	AE Rate	E-cig (16mg)	NRT (21mg Patch)	6	137 events among 107 persons	NA	0.8 events per person month	119 events among 96 persons	NA	0.8 events per person month	IRR 1.05 (0.82, 1.34) p=0.7
			E-cig (16mg)	Placebo (0mg E-cig)	6	137 events among 107 persons	NA	0.8 events per person month	36 events among 26 persons	NA	0.9 events per person month	NR
		Participants with AEs	E-cig (16mg)	NRT (21mg Patch)	6	107	289	37.0%	96	295	32.5%	NR
			E-cig (16mg)	Placebo (0mg E-cig)	6	107	289	37.0%	26	73	35.6%	NR
Caponnetto, 2013[145] ECLAT Fair	General	AE Rate	E-cig (both study groups)‡	Placebo (0mg E-cig)	3	NR	200	NR	NR	100	NR	NR No difference was found in frequency or distribution of AEs between study groups
			E-cig (both study groups)‡	Placebo (0mg E-cig)	12	NR	200	NR	NR	100	NR	NR No difference was found in frequency or distribution of AEs between study groups
		Serious AEs*	E-cig (both study groups)‡	Placebo (0mg E-cig)	12	0	200	NA	0	100	NA	NA

Table 9. Adverse Event Results (KQ 3) for Primary Evidence on the Use of Electronic Cigarettes for Tobacco Cessation

Author, Year Quality	System or organ class	Outcome	IG	CG	FU (mo)	IG events	IG N	IG AE rate	CG events	CG N	CG AE rate	Effect estimate (95% CI)
Carpenter, 2017[147] Fair	General	AE Rate	E-cig (16mg)	No Intv	4	17 events among 9 persons	25	NR	29 events among 8 persons	22	NR	NR
			E-cig (24mg)	No Intv	4	21 events among 11 persons	21	NR	29 events among 8 persons	22	NR	NR
		Participants with AEs	E-cig (16mg)	No Intv	4	9	25	36%	8	22	36%	NR
			E-cig (24mg)	No Intv	4	11	21	52%	8	22	36%	NR
Cravo, 2016[148] Fair	General	AE Rate	E-cig (2.7 mg)	No Intv	3	1515 events among 271 persons	306	NR	225 events among 80 persons	102	NR	NR
		Serious AEs	E-cig (2.7 mg)	No Intv	3	5 events among 5 persons	306	NR	0	102	0	NR
	Respiratory	Coughing	E-cig (2.7 mg)	No Intv	3	52	306	17.0%	8	102	7.8%	NR
		Sore Throat	E-cig (2.7 mg)	No Intv	3	85	306	27.8%	9	102	8.8%	NR
		Sinus Infection	E-cig (2.7 mg)	No Intv	3	34	306	11.1%	8	102	7.8%	NR
	Neurologic	Headache	E-cig (2.7 mg)	No Intv	3	145	306	47.4%	34	102	33.3%	NR

Table 9. Adverse Event Results (KQ 3) for Primary Evidence on the Use of Electronic Cigarettes for Tobacco Cessation

Author, Year Quality	System or organ class	Outcome	IG	CG	FU (mo)	IG events	IG N	IG AE rate	CG events	CG N	CG AE rate	Effect estimate (95% CI)
Hajek, 2019[154] TEC Fair	General	Serious AE incidence	E-cig (any)	NRT (any)	12	27	438	6.2%	22	446	4.9%	NR
	Respiratory	Coughing	E-cig (any)	NRT (any)	12	97	314	30.8%	111	279	39.8%	RR 0.8 (0.6, 0.9)
		Shortness of breath	E-cig (any)	NRT (any)	12	66	314	21.0%	64	279	22.9%	RR 0.9 (0.7, 1.1)
		Wheezing	E-cig (any)	NRT (any)	12	74	314	23.5%	59	279	21.1%	RR 1.1 (0.8, 1.4)
		Throat/ mouth irritation	E-cig (any)	NRT (any)	12	286	438	65.3%	221	432	51.1%	RR 1.27 (1.13, 1.43)
		Phlegm	E-cig (any)	NRT (any)	12	79	314	25.1%	103	279	36.9%	RR 0.7 (0.6, 0.9)
	Gastro-intestinal	Nausea	E-cig (any)	NRT (any)	12	137	438	31.3%	169	446	37.9%	RR 0.83 (0.69, 0.99)
	Psychiatric	Disturbed Sleep	E-cig (any)	NRT (any)	12	279	438	63.7%	303	446	67.9%	RR 0.94 (0.98, 1.04)
Lee, 2019[157] Fair	General	Number of participants with any AE	E-cig	NRT, gum	6	5	75	6.7	13	75	17.3	p= 0.044
Masiero, 2017[146] Fair	Respiratory	Cough	E-cig (8mg)	Placebo (0mg E-cig)	3	7	70	10.0%	2	70	2.9%	NR
		Dyspnea	E-cig (8mg)	Placebo (0mg E-cig)	3	0	70	NA	1	70	1.4%	NR
		Burning throat	E-cig (8mg)	Placebo (0mg E-cig)	3	4	70	5.7%	2	70	2.9%	NR
	Neurologic	Headache	E-cig (8mg)	Placebo (0mg E-cig)	3	0	70	NA	0	70	NA	NR
	Gastro-intestinal	Nausea	E-cig (8mg)	Placebo (0mg E-cig)	3	1	70	1.4%	2	70	2.9%	NR
		Stomach-ache	E-cig (8mg)	Placebo (0mg E-cig)	3	0	70	NA	0	70	NA	NR
	Psychiatric	Insomnia	E-cig (8mg)	Placebo (0mg E-cig)	3	1	70	1.4%	0	70	NA	NR
		Confusion	E-cig (8mg)	Placebo (0mg E-cig)	3	1	70	1.4%	0	70	NA	NR
Tseng, 2016[150] Fair	General	Participants with AEs	E-cig	Placebo	3 wk	11	50	22.5%	5	49	10.3%	p=0.14

Table 9. Adverse Event Results (KQ 3) for Primary Evidence on the Use of Electronic Cigarettes for Tobacco Cessation

Author, Year Quality	System or organ class	Outcome	IG	CG	FU (mo)	IG events	IG N	IG AE rate	CG events	CG N	CG AE rate	Effect estimate (95% CI)
Walker, 2019[155] Fair	General	Serious AEs	E-cig (18mg) +NRT (21mg)	Placebo (0mg E-cig) + NRT (21mg)	6	18 events in 16 people	500	4.0%	27 events in 22 people	499	5.0%	IRR 0.66 (0.36, 1.20); p=0.18
			E-cig (18mg) +NRT (21mg)	NRT (21mg)	6	18 events in 16 people	500	4.0%	4 events in 3 people	125	3.0%	IRR 0.86 (0.29, 2.53); p=0.78

Note: No intervention control groups continued smoking with conventional cigarettes and received no behavioral intervention component.
* Defined as any event requiring unscheduled visits to a physician or hospitalization.
‡Group A=7.2 mg E-cig for 12 weeks; Group B=7.2 mg E-cig for 6 weeks and 5.4 mg E-cig for 6 weeks.

Abbreviations: AE = adverse event; E-cig = electronic cigarette; Intv = intervention; NA = not applicable; NR = not reported; NRT = nicotine replacement therapy; RR = relative risk

Table 10. Primary Evidence on Pharmacotherapy Among Pregnant Individuals: Study and Population Characteristics, by Study Design

Study design	Author, Year Trial name Quality	Country	N rand	Brief population/cohort description	Intervention/ Exposure	Comparison	Outcomes of interest
RCT	Berlin, 2014[167] SNIPP Good	France	403	Pregnant smokers aged 18 years or more with a gestational age of between nine and 20 weeks of amenorrhea who smoked at least five cigarettes a day and were motivated to quit	NRT patch (10-15 mg/day) plus behavioral support	Placebo patch plus behavioral support	• Low BW • Mean BW • Preterm birth • Stillbirth • Tobacco cessation
	Coleman, 2012[168] SNAP Good	UK	1051	Pregnant smokers aged 16–50 years, between 12 and 24 weeks' pregnant, smoked at least 10 cigarettes per day before pregnancy and continued to smoke at least five cigarettes per day	NRT patch (15 mg/ 16 hrs) plus behavioral counseling	Placebo patch plus behavioral counseling	• Low BW • Mean BW • Preterm birth • Stillbirth • Tobacco cessation
	Oncken, 2008[174] Fair	US	194	Pregnant smokers, ≤26 weeks pregnant and smoked ≥ 1 cpd	NRT gum (2 mg) plus behavioral counseling	Placebo gum plus behavioral counseling	• Low BW • Mean BW • Preterm birth • Stillbirth • Tobacco cessation
	Oncken, 2019[175] Fair	US	154	Pregnant women who smoked ≥5 cigarettes daily	NRT inhaler (10mg) plus behavioral counseling	Placebo inhaler plus behavioral counseling	• Low BW • Mean BW • Preterm birth • Tobacco cessation
	Wisborg, 2000[178] Fair	Denmark	250	Pregnant smokers, who smoked ≥ 10 cigarettes after first trimester	NRT patch (15 mg/ 16 hrs for 8 weeks, 10 mg/16 hrs for 3 weeks) plus behavioral counseling	Placebo patch plus behavioral counseling	• Low BW • Mean BW • Preterm birth • Tobacco cessation

Table 10. Primary Evidence on Pharmacotherapy Among Pregnant Individuals: Study and Population Characteristics, by Study Design

Study design	Author, Year Trial name Quality	Country	N rand	Brief population/cohort description	Intervention/ Exposure	Comparison	Outcomes of interest
Non-placebo control RCT	El-Mohandes, 2013[171] Fair	US	52	Pregnant African American smokers ≥18 years, and <30 weeks pregnant with a desire to quit	Trans-dermal NRT, 14-21mg for 10 wks depending on cpd. Maximum of six clinical visits.	Behavioral counseling	• Low BW • Mean BW • Preterm birth • Tobacco cessation
	Pollak, 2007[176] Baby Steps Fair	US	181	Pregnant smokers between 13 and 25 weeks pregnant and smoked ≥ 5 CPD	Choice of NRT from patch (7-12mg/ 16hrs depending on cpd), gum (2mg/each cpd), or lozenge (2mg/ each cpd) plus behavioral counseling	Behavioral counseling	• Low BW • Mean BW • Preterm birth • Tobacco cessation
Cohort	Berard, 2016[179] Quebec Pregnancy Cohort Good	Canada	1288	Quebec Pregnancy Cohort data	Bupropion alone with or without smoking or NRT patch alone with or without smoking	Smokers without bupropion or NRT patch exposure	• Preterm birth
	Dhalwani, 2018[180, 181] The Health Improvement Network (THIN) Fair	UK	220,630	Cohort of singleton pregnancies ending in live or stillbirth between 2001 and 2012 from The Health Improvement Network UK general practice database	NRT (any)	Smokers and non-smokers	• Stillbirth • Major congenital anomalies
	Pedersen, 2019[182] Good	Denmark, Sweden	885,185	Nationwide health and administrative registry data for cohort including live-born and stillborn infants from 1 May 2007 to 31 December 2012	Dispensed varenicline	1) Unexposed to varenicline, but exposed to maternal smoking in utero or 2) unexposed to varenicline and unexposed to maternal smoking in utero)	• Major congenital malformations • Stillbirth • Fetal growth restriction • Preterm birth • Sudden infant death syndrome
	Tran, 2020[183] Smoking MUMS study	Australia	1,014,731	Smoking MUMS cohort; perinatal and pharmaceutical dispensing	Bupropion, varenicline or NRT during pregnancy	Women who had never been exposed	• Any adverse perinatal event*

Table 10. Primary Evidence on Pharmacotherapy Among Pregnant Individuals: Study and Population Characteristics, by Study Design

Study design	Author, Year Trial name Quality	Country	N rand	Brief population/cohort description	Intervention/ Exposure	Comparison	Outcomes of interest
	Good			data for all deliveries in New South Wales and Western Australia between 2003 and 2012.		to any of these medicines in pregnancy	• Major congenital anomaly
	Zhu, 2014[184] Danish National Birth Cohort (DNBC) Good	Denmark	84,803	Danish National Birth Cohort data	NRT (mother) plus smoker (father) or NRT (mother) plus non-smoker (father)	Nonsmoker (mother) plus nonsmoker (father)	• ADHD (child)

* Any adverse perinatal event was a composite of 10 individual birth outcomes, including preterm birth (< 37 weeks, medically indicated or spontaneous), small for gestational age (SGA, birthweight < 10th percentile sex- and gestational age-specific), Apgar score at 5 min < 7, admission to neonatal special care (NSC), severe neonatal morbidity complications, emergency caesarean section, severe maternal morbidity complications, preterm premature rupture of membranes (PPROM), placental abruption and perinatal death (stillbirth or 28-day neonatal death).

Abbreviations: ADHD = attention deficit/hyperactivity disorder; BW = birth weight; CG = control group; CPD = cigarettes per day; hr = hour(s); IG = intervention group; NRT = nicotine replacement therapy; mg = milligram(s); RCT = randomized controlled trial; UK = United Kingdom; US = United States

Table 11. Summary of Perinatal Health Outcome Results (KQ 1) of Behavioral Tobacco Cessation Interventions Among Pregnant Women, Psychosocial Interventions vs. Any Control (Within Chamberlain, 2017 Review[185])

Outcome	Intervention	K	Total n analyzed	IG events	IG n	CG events	CG n	Risk Ratio (95% CI)	I^2
Mean birthweight*	Any psychosocial intervention	26	11,338	3207.5	5756	3146.9	5582	MD=55.60 (29.82, 81.38)	31%
	Counseling	14	5471	3080.7	2698	3744.9	2733	MD=42.17 (11.79, 72.55)	0%
	Health education	2	1172	3330.9	685	3255.1	487	MD=27.35 (-53.88, 108.58)	33%
	Feedback	2	3006	3418.7	1501	3221.1	1505	MD=79.43 (-53.05, 211.91)	58%
	Incentives	6	834	3150.5	451	3088.2	383	MD=114.01 (63.91, 164.11)	23%
	Social support	1	142	3100	67	3072	75	MD=28.0 (-152.48, 208.48)	NA
	Exercise	1	713	3132.4	354	3146.8	359	MD=-14.40 (-104.15, 75.35)	NA
Low birthweight	Any psychosocial intervention	18	9402	355	4743	429	4659	0.83 (0.72, 0.94)	0%
	Counseling	8	7339	151	2090	200	2249	0.83 (0.68, 1.01)	0%
	Health education	2	1172	40	685	37	487	0.87 (0.49, 1.55)	40%
	Feedback	1	2848	99	1423	121	1425	0.82 (0.63, 1.06)	NA
	Incentives	5	252	22	156	21	96	0.63 (0.37, 1.08)	0%
	Social support	1	79	5	36	6	43	1.00 (0.33, 2.99)	NA
	Exercise	1	712	38	353	44	359	0.88 (0.58, 1.32)	NA
Preterm births	Any psychosocial intervention	19	9222	337	4705	363	4517	0.93 (0.77, 1.11)	18%
	Counseling	8	3447	99	1672	117	1775	0.93 (0.71, 1.20)	0%
	Health education	2	1170	29	684	25	486	0.92 (0.55, 1.56)	40%
	Feedback	2	3111	115	1572	150	1539	0.60 (0.28, 1.29)	63%
	Exercise	1	704	35	356	26	348	1.32 (0.81, 2.14)	NA
	Incentives	6	790	59	421	45	369	0.91 (0.52, 1.59)	33%
Stillbirths	Any psychosocial intervention	8	6170	40	3053	33	3117	1.20 (0.76, 1.90)	0%
	Counseling	5	2454	16	1197	14	1257	1.14 (0.55, 2.33)	0%
	Feedback	2	2960	22	1479	17	1481	1.28 (0.69, 2.39)	0%
	Exercise	1	756	2	377	2	379	1.01 (0.14, 7.10)	NA

* Presented as mean in grams; weighted means (g) calculated

Abbreviations: CG = control group; CI = confidence intervals; IG = intervention group; MD = mean difference; NA = not applicable

Table 12. Summary of Tobacco Cessation Outcomes (KQ 2) of Behavioral Tobacco Cessation Interventions Among Pregnant Women (Within Chamberlain, 2017 Review[185])

Intervention	Control	K	N analyzed	IG	IG N	IG quit rate	CG	CG N	CG quit rate	Risk ratio (95% CI)	I^2
Any psychosocial intervention	Any control	97	26,637	2332	14,192	16.4%	1518	12,445	12.2%	1.35 (1.23, 1.48)	44%
Counseling	Any control	51	18,276	1376	9510	14.5%	950	8766	10.8%	1.31 (1.16, 1.47)	40%
Health education	Any control	11	2142	195	1275	15.3%	107	867	12.3%	1.22 (0.97, 1.55)	7%
Feedback	Any control	6	859	94	513	18.3%	31	346	9.0%	1.92 (1.16, 3.17)	7%
Incentives	Any control	13	1752	222	995	22.3%	89	757	11.8%	1.88 (1.12, 3.14)	66%
Social support	Any control	14	2629	405	1409	28.7%	310	1220	25.4%	1.16 (0.96, 1.40)	23%
Exercise	Any control	1	785	30	392	7.7%	25	393	6.4%	1.20 (0.72, 2.01)	NA
Other (behavioral)	Any control	1	194	10	98	10.2%	6	96	6.3%	1.63 (0.62, 4.32)	NA
Counseling	Usual care	30	12,432	771	6350	12.1%	546	6082	9.0%	1.44 (1.19, 1.73)	49%
	Less intensive intervention	18	5657	494	2897	17.1%	368	2760	13.3%	1.25 (1.07, 1.47)	28%
	Alterative intervention	1	257	58	128	4.5%	51	129	4.0%	1.15 (0.86, 1.53)	NA
Health education	Usual care	5	629	41	310	13.2%	25	319	7.8%	1.59 (0.99, 2.55)	0%
	Less intensive intervention	4	1282	116	759	15.3%	72	523	13.8%	1.20 (0.85, 1.70)	33%
	Alterative intervention	1	31	2	16	12.5%	1	15	6.7%	1.88 (0.19, 18.60)	NA
Feedback	Usual care	2	355	33	198	16.70%	6	157	3.80%	4.39 (1.89, 10.21)	0%
	Less intensive intervention	3	439	42	276	15.2%	19	163	11.7%	1.29 (0.75, 2.20)	0%
Incentives	Usual care	5	NR	NR	NR	NR	NR	NR	NR	NR, subtotals only	NR
Social support	Less intensive intervention	7	781	102	405	25.2%	73	376	19.4%	1.21 (0.93, 1.58)	0%
Exercise	Usual care	1	785	30	392	7.7%	25	393	6.4%	1.21 (0.72, 2.01)	NA

Abbreviations: CG = control group; CI = confidence intervals; IG = intervention group; NA = not applicable; NR = not reported

Table 13. Summary of Evidence for the General Adult Population

Key question	Intervention	Number of included studies and participants*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
1: Health outcomes	Combined pharm and behavioral	0	NA	NA	NA	Insufficient	NA
	Pharm	0	NA	NA	NA	Insufficient	NA
	Behavioral	1 review (1 RCT, n=1445)	One trial found favorable effects on all-cause and coronary disease mortality and lung cancer incidence and mortality 20 years following an intensive behavioral intervention, although results were not statistically significant.	NA	Only one review reported the results of one intervention in men. Within that trial, the rate of smoking among control group participants declined steadily over the followup period, narrowing the intervention effect.	Low evidence of potential benefit	One trial conducted among civil servant men aged 40-59 years in the UK with high risk of cardiorespiratory disease. Intervention took place in the 1970's.
	Electronic cigarettes	0 RCTs	NA	NA	NA	Insufficient	NA
2: Cessation outcomes	Combined pharm and behavioral	1 review (53 RCTs, n=25,375)	Combined pharmacotherapy and behavioral interventions increased smoking quit rates by 68-98% compared with no or minimal treatment (RR 1.83 [95% CI, 1.68 to 1.98]) at 6 months or more followup.	Reasonably consistent Reasonably precise	May be risk of bias due to lack of blinding of participants.	High evidence of benefit‡	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.

Table 13. Summary of Evidence for the General Adult Population

Key question	Intervention	Number of included studies and participants*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
	Pharm	5 reviews (336 RCTs, n>159,000)	NRT, bupropion, and varenicline significantly increased the chances of quitting smoking compared with placebo or no medication. Reviews suggested that NRT might increase smoking abstinence at 6 months or longer by 49-61% (RR 1.55 [95% CI, 1.49 to 1.61]); bupropion by 49-76% (RR 1.62 [95% CI, 1.49 to 1.76]); and varenicline by 106-143% (RR 2.24 [95% CI, 2.06 to 2.43]). Absolute quit differences averaged 6.4% for NRT; 8.2% for bupropion, and 14.5% for varenicline. Using a combination of NRT products increased quitting more than the use of a single NRT product (RR 1.25 [95% CI, 1.15 to 1.36]). Direct comparisons between drugs suggested that varenicline may be superior to NRT and bupropion in achieving smoking abstinence at 6 months or longer.‖	Reasonably consistent Reasonably precise	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 for each type of drug.	High evidence of benefit§	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.

Table 13. Summary of Evidence for the General Adult Population

Key question	Intervention	Number of included studies and participants*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
	Behavioral	20 reviews (830 RCTs, n>500,000)	Health provider advice and counseling, individual counseling, group-based interventions, telephone counseling, mobile phone-based interventions, tailored and interactive internet-based interventions, and incentives showed significant increased smoking cessation at 6 or more months relative to controls (15% to 88%). For example, for physician advice versus minimal controls or usual care: RR 1.76 (95% CI, 1.58 to 1.96). Providing more intense adjunctive behavioral support to smokers receiving pharmacotherapy may increase cessation by 8-22% (RR 1.15 [95% CI, 1.08 to 1.22]). Evidence on the use of motivational interviewing, decision aids, print-based, nontailored self-help materials, real-time video counseling, biomedical risk assessment, exercise, complementary and alternative therapies, and system-level interventions was limited and not definitive in the effects on cessation.	Reasonably consistent Reasonably precise	Individual trials may be represented in more than one review and/or meta-analysis. Indication of possible publication bias for evidence related to motivational interviewing and acupuncture. Fixed-effects models were used in nearly all meta-analyses.	Moderate to High evidence of benefit¶	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.

Table 13. Summary of Evidence for the General Adult Population

Key question	Intervention	Number of included studies and participants*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
	Relapse prevention	1 review (77 RCTs, n=67,285)	Analyses of behavioral interventions among abstainers did not detect an effect in both studies of assisted abstainers (RR 0.99 [95% CI, 0.87 to 1.13]; I^2=56%; k=10; n=5408) and unaided abstainers (RR 1.06 [95% CI, 0.96 to 1.16]; I^2=1%; k=5; n=3561) from the general population. There was some evidence that extending varenicline could be beneficial in preventing relapse, but it was only reported by two studies. NRT was found to help in unassisted abstainers, but no difference was seen among those who achieved abstinence with NRT. None of the six studies that examined the use of bupropion to prevent relapse found a statistically significant effect.	Inconsistent Imprecise	Highly variable study designs and included interventions.	Moderate evidence of no benefit of behavioral interventions on relapse prevention Moderate evidence of benefit of varenicline on relapse prevention; low evidence of no benefit of bupropion or NRT on relapse prevention	Studies were highly heterogenous and may not be applicable to the general adult population.

Table 13. Summary of Evidence for the General Adult Population

Key question	Intervention	Number of included studies and participants*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
	Electronic cigarettes	5 RCTs (n=3117)	Two trials (n=2008) found statistically significantly greater rates of smoking abstinence in those using e-cigarettes containing nicotine (with or without the co-use of NRT) compared with NRT alone or NRT plus non-nicotine e-cigarettes at 6- to 12-months followup, although continued use of e-cigs remained high after the treatment phase. Another 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 (p=0.04), but 27 percent of those who quit smoking continued to use e-cigarettes at 1 year. The remaining two trials 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=807).	Inconsistent Imprecise	Limited statistical power to detect differences and differential loss to followup in all five trials (22-50%). Wide variance of nicotine concentrations in e-cig interventions (7.8mg vs. 18mg)	Insufficient	All five trials took place outside of the US, Korea, in New Zealand, Italy, and the UK. Two trials used older models of e-cigs of which is no longer available. One trial conducted among smokers not wanting to quit.
3: Harms	Combined pharm and behavioral	0 reviews#	NA	NA	NA	Moderate evidence of no harms	NA
	Pharm	15 reviews#	NRT, bupropion, and varenicline were not associated with an increased risk in major CV or neuropsychiatric adverse events. NRT was associated with a higher rate of any CV adverse events largely driven by low-risk events, typically bradycardia and arrhythmia. There was no evidence of a difference in harms associated with medications for	Reasonably consistent Reasonably precise	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	Moderate evidence of no serious harms	Findings appear applicable across populations and settings, including among patients with severe mental illness.

Table 13. Summary of Evidence for the General Adult Population

Key question	Intervention	Number of included studies and participants*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
			those with versus without severe mental illness.		underreporting.		
	Behavioral	3 reviews#	There was no evidence that behavioral tobacco cessation interventions are associated with serious adverse events.	NA	Very few reviews assessed AEs related to behavioral interventions.	Moderate evidence of no harms**	Limited evidence on harms limits applicability.
	Electronic cigarettes	9 RCTs (n=3942)	No trials reported serious AEs in either the intervention or control groups related to product use and no significant differences in the frequency of AEs among study groups. Coughing, nausea, throat irritation and sleep disruption were the most commonly reported side effects of e-cig use.	Reasonably consistent Imprecise	Limited statistical power to detect differences and differential loss to followup in all three trials (22-39%). One study did not report methods for AEs reporting.	Insufficient	The two US trials had the lowest enrollment (<100 participants). Two trials used older models of e-cigs, one of which is no longer available, one trial used an e-cig that is not available in US markets, and one trial used a prototype.

* Number of included studies reflects the number of systematic reviews designated as primary evidence for that body of evidence as well as the summed total number of included studies and observations from each review.

† For our review-of-reviews method, we adopted the strength of the overall body of evidence assigned within the primary systematic review. In most cases, these grades were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group definitions which consider study limitations, consistency of effect, imprecision, indirectness and publication bias. Where strength of evidence grades were not available, we adapted the EPC approach to assign an overall strength of evidence grade based on consensus discussions involving at least two reviewers.[78]

‡ Some evidence of asymmetry in a funnel plot; excess of small trials detecting larger effects. However, in a sensitivity analysis, removing smaller studies did not markedly decrease the pooled estimate.

§ Sensitivity analysis including only those studies judged to be a low risk of bis did not impact the pooled results for any comparison; for NRT and bupropion, the funnel plots showed some evidence of asymmetry. However, given the large number of trials in these reviews, this does not suggest the results would be altered significantly were smaller studies with lower RRs included.

‖ Evidence from existing systematic reviews as well as the EAGLES trial indicate that adult smokers randomized to varenicline have a statistically significant higher likelihood of quitting smoking at 6 months compared with those randomized to NRT or bupropion. In the EAGLES trial (n=8144) 21.8% of smokers randomized to varenicline quit smoking at 6 months compared with 15.7% randomized to NRT (OR 1.52 [95% 1.29 to 1.78]) and 16.2% randomized to bupropion (OR 1.45 [95% CI, 1.24 to 1.70]).[161]

¶ Quality of the evidence differs for each specific type of intervention, but generally reflects moderate to high certainty grades. Most common reasons for downgraded the quality of evidence were unexplained statistical heterogeneity, several studies with high or unclear risk of bias, or inconsistency in the evidence base.

Total number of studies and observations not estimated

Table 13. Summary of Evidence for the General Adult Population

** Despite the relatively limited number of reviews that reported harms related to interventions, we are moderately confident that there are no serious harms related to combined pharmacotherapy and behavioral counseling interventions or behavioral counseling alone for tobacco cessation.

Abbreviations: AE = adverse event; CI = confidence interval; CV = cardiovascular; e-cig = electronic cigarette; mg = milligrams; NA = not applicable; NRT = nicotine replacement therapy; pharm = pharmacotherapy; RCT = randomized controlled trial; RR = risk ratio; UK = United Kingdom; US = United States

Table 14. Summary of Evidence for Pregnant Women

Key Question	Intervention	Number of included studies*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
1: Health outcomes	Pharm	7 RCTs (n=2285)	Limited evidence of NRT on perinatal and child health benefits. Five placebo controlled NRT trials reported preterm births with the three largest trials reporting effects close to null and two reporting reduced risk with NRT. These five trials also reported birthweight; the two largest placebo-controlled trials reported no difference with NRT, and two trials reported higher mean birthweights associated with NRT. The risk for low birthweight was lower in the smallest trial, and results were mixed but null for the others. 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%; OR 1.40 [95% CI 1.05 to 1.86]). No trials of bupropion or varenicline among pregnant women.	Inconsistent Imprecise	Rare health outcomes and few trials of NRT limited statistical precision and ability to draw conclusions. Limited information on the women approached for participation that declined, and low participation rates. Timing of the final antenatal assessment varied considerably among trials which may affect the amount of time women were exposed to the intervention as well as those lost to followup and measurement of perinatal outcomes.	Insufficient evidence for birth outcomes and child health outcomes	Trials mainly conducted in high-income countries including the US, relevant and applicable. Pharmacotherapy trials were mostly 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	1 review (26 RCTs, n=12,338)	Suggestive benefit of behavioral interventions on mean birthweight (mean difference, 55.60 [95% CI, 29.82 to 81.38])	Reasonably consistent Reasonably precise		High evidence of potential benefit on mean birthweight and risk of preterm	

Table 14. Summary of Evidence for Pregnant Women

Key Question	Intervention	Number of included studies*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
			and low birthweight (RR 0.83 [95% CI 0.72 to 0.94]), vs. usual care or control. Uncertain evidence on the effect of behavioral interventions on preterm birth (RR 0.93 [95% CI, 0.77 to 1.11]) and stillbirths (RR 1.20 [95% CI, 0.76 to 1.90]).			birth	
	Electronic cigarettes	0	NA	NA	NA	Insufficient	NA
2: Cessation outcomes	Pharm	7 RCTs (n=2285)	No statistical evidence of NRT efficacy for validated smoking cessation in late pregnancy (RR 1.11, 95% CI 0.79 to 1.56) in pooled analysis of five placebo-controlled trials. Limited power, and all trials in the direction of benefit including two trials with no NRT control conditions. No trials of bupropion or varenicline among pregnant women.	Reasonably consistent Imprecise	Limited information on the women approached for participation that declined, and low participation rates.	Low evidence of no benefit	Trials mainly conducted in high-income countries including the US, relevant and applicable. Pharmacotherapy trials were mostly 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
	Behavioral	1 review (97 RCTs, n=26,637)	The pooled estimate from 97 trials suggested an increased risk of quitting smoking in late pregnancy for psychosocial interventions compared with controls (RR 1.35 [95% CI, 1.23 to 1.48]), with a similar benefit	Reasonably consistent Reasonably precise	Minimal information on the number of women who were eligible for inclusion or were approached to take place in the trials.	Moderate evidence of benefit	

Table 14. Summary of Evidence for Pregnant Women

Key Question	Intervention	Number of included studies*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
			when limited to the most common intervention (counseling) versus usual care (RR 1.44 [95% CI 1.19 to 1.73]) Heterogeneity was moderate for the pooled effect (44%), but there was no definitive evidence of subgroup effects by study, population, or intervention characteristics.		Timing of the final antenatal assessment of smoking status varied considerably among trials which may affect the amount of time women were exposed to the intervention as well as those lost to followup.		who disclose smoking status and willing to participate in trials may differ from general population (e.g., motivation to quit).
	Relapse prevention	1 review (18 RCTs, n=5545)	No clear clear benefit on relapse prevention at the end of pregnancy (RR 1.05 [95% CI, 0.99 to 1.11]; k=8; n=1523; I^2=0%) or during the postpartum period (RR 1.02 [95% CI, 0.94 to 1.09]; k=15; n=4606; I^2=3%).	Inconsistent Imprecise	Variable interventions tested	Low evidence of no benefit of behavioral interventions	
	Electronic cigarettes	0	NA	NA	NA	Insufficient	NA
KQ3: Harms	Pharm	7 RCTs (n=2285) 5 cohort studies (n=1,293,379)	Limited evidence of perinatal harms from NRT; mixed findings on birth outcomes from trials, but most in direction of benefit rather than harm (KQ 1). Two-year followup from one NRT trial did not suggest harms (KQ 1). No trials of bupropion or varenicline among pregnant women.	Inconsistent Imprecise	Few trials of NRT and not all reported consistently on health outcomes and adverse events. Observational studies may not be able to fully account for confounding, substantial	Low evidence of no harm	Trials mainly conducted in high-income countries including the US, relevant and applicable.

Table 14. Summary of Evidence for Pregnant Women

Key Question	Intervention	Number of included studies*	Summary of findings	Consistency and precision	Other limitations	Strength of evidence†	Applicability
			Observational evidence did not indicate harms of major congenital anomalies, stillbirth, premature birth, or low birthweight associated with NRT, bupropion, or varenicline.		differences across a range of population characteristics among comparison groups.		
	Behavioral	1 review (13 RCTs, n=5831)	There did not appear to be any adverse effects from the psychosocial interventions. Five of 13 trials evaluating psychological impact reported an improvement in women's psychological well-being and none reported a negative impact.	Reasonably consistent Reasonably precise	Measures of adverse events rarely reported; most reliant on passive reporting.	Moderate evidence of no harm	
	Electronic cigarettes	0	NA	NA	NA	Insufficient	NA

* Number of included studies reflects the number of systematic reviews designated as primary evidence for that body of evidence as well as the summed total number of included studies and observations from each review.

† For our review-of-reviews method, we adopted the strength of the overall body of evidence assigned within the primary systematic review. In most cases, these grades were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group definitions which consider study limitations, consistency of effect, imprecision, indirectness and publication bias. Where strength of evidence grades were not available, we adapted the EPC approach to assign an overall strength of evidence grade based on consensus discussions involving at least two reviewers.[78]

Abbreviations: NA = not applicable; NRT = nicotine replacement therapy; pharm = pharmacotherapy; US = United States; vs = versus

Appendix A. Detailed Methods

Literature search strategies for overview of reviews: Tobacco cessation in adults

Sources searched (2014-present):
Agency for Healthcare Research and Quality
Canadian Agency for Drugs and Technologies in Health
Cochrane Database of Systematic Reviews
Community Guide
Database of Abstracts of Reviews of Effects
Health Technology Assessment
Health and Medicine Division (HMD) of the National Academies of Sciences, Engineering, and Medicine (formerly Institute of Medicine)
NHS Health Technology Assessment Programme
PsycINFO
PubMed
Surgeon General

Canadian Agency for Drugs and Technologies in Health
Pharmacological based strategies for Smoking Cessation (2016)
https://cadth.ca/pharmacologic-based-strategies-smoking-cessation

Integrated cessation program for adults who smoke cannabis and tobacco: Clinical effectiveness and guidelines (2017)
https://cadth.ca/sites/default/files/pdf/htis/2017/RA0934%20Interventions%20for%20Cannabis%20Use%20Disorder%20and%20Co-smokers%20Final.pdf

Smoking cessation interventions for patients with severe mental illnesses: A review of clinical effectiveness and guidelines (2017)
https://cadth.ca/sites/default/files/pdf/htis/2017/RC0922%20Smoking%20Cessation%20in%20Mental%20Illness%20Final.pdf

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#1	tobacco:ti	1800
#2	smoking:ti	8736
#3	smoker*:ti	3237
#4	smokeless:ti	167
#5	nicotine:ti	2830
#6	cigar*:ti	1822
#7	(vape or vaping or vapour):ti	148
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7 with Cochrane Library publication date Between Jan 2014 and Dec 2019, in Cochrane Reviews, Cochrane Protocols	67

NHS HTA Programme
Pharmacological interventions for promoting smoking cessation during pregnancy 2018 [in progress]
https://www.journalslibrary.nihr.ac.uk/programmes/sr/NIHR128783/#/

Relapse prevention interventions for smoking cessation (2019) [waiting to start]

https://www.journalslibrary.nihr.ac.uk/programmes/sr/NIHR128787/#/

The Filter FE Challenge: pilot trial and process evaluation of a multi-level smoking prevention intervention in further education settings (2017)
https://www.journalslibrary.nihr.ac.uk/programmes/phr/134202/#/

A multi-centred Trial of physical Activity assisted Reduction of Smoking (TARS) (2017)
https://www.journalslibrary.nihr.ac.uk/programmes/hta/1511101/#/

Evaluating Long-term Outcomes of NHS Stop Smoking Services (ELONS) (2015)
https://www.journalslibrary.nihr.ac.uk/programmes/hta/0916101/#/

Helping pregnant smokers quit: Multi-centre RCT of electronic cigarettes vs usual care. (2017)[in progress]
https://www.journalslibrary.nihr.ac.uk/programmes/hta/155785/#/

A randomised controlled trial to examine the efficacy of e-cigarettes compared with nicotine replacement therapy, when used within the UK stop smoking service (2014) [waiting to publish]
https://www.journalslibrary.nihr.ac.uk/programmes/hta/12167135/#/

A randomised trial to increase the uptake of smoking cessation services using Personal Targeted risk information and Taster Sessions (2017)
https://www.journalslibrary.nihr.ac.uk/programmes/hta/085802/#/

Barriers and facilitators to smoking cessation in pregnancy and following childbirth: literature review and qualitative study (2017)
https://www.journalslibrary.nihr.ac.uk/programmes/hta/119301/#/

Exploring the uptake and use of electronic cigarettes provided to smokers accessing homeless centres: a feasibility study (2018) [in progress]
https://www.journalslibrary.nihr.ac.uk/programmes/phr/174429/#/

A pragmatic randomised controlled trial of physical activity as an aid to smoking cessation during pregnancy. (2015)
https://www.journalslibrary.nihr.ac.uk/programmes/hta/070114/#/

Feasibility randomised controlled trial of a smoking cessation smartphone app that delivers 'context aware' behavioural support in real time (2019)
https://www.journalslibrary.nihr.ac.uk/programmes/phr/179231/#/

The London Exercise And Pregnant smokers (LEAP) trial: a randomised controlled trial of physical activity for smoking cessation in pregnancy with an economic evaluation (2015)
https://www.journalslibrary.nihr.ac.uk/hta/hta19840/#/abstract

Nicotine preloading for smoking cessation: the Preloading RCT (2018)
https://www.journalslibrary.nihr.ac.uk/hta/hta22410/#/abstract

Smoking Cessation Intervention for Severe Mental Ill Health Trial (SCIMITAR): a definitive randomised evaluation of a bespoke smoking cessation service (2015)
https://www.journalslibrary.nihr.ac.uk/programmes/hta/1113652/#/

Mixed methods systematic review to identify the determinants of nicotine replacement therapy use and of vaping in pregnancy (2018)
https://www.journalslibrary.nihr.ac.uk/programmes/sr/NIHR128785/#/

PubMed search strategy

Search	Query
#11	Search #8 OR #10
#10	Search #7 AND #9 AND ("2014"[Date - Publication] : "3000"[Date - Publication]) AND English[Language]
#9	Search (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])
#8	Search #7 AND systematic[sb] AND ("2014"[Date - Publication] : "3000"[Date - Publication]) AND English[Language]
#7	Search #4 NOT #6
#6	Search ("Child"[Mesh] OR "Adolescent"[Mesh]) NOT #5
#5	Search ("Adult"[Mesh]) AND ("Child"[Mesh] OR "Adolescent"[Mesh])
#4	Search #1 OR (#2 AND #3)

Appendix A. Detailed Methods

Search	Query
#3	Search (cessat*[tiab] OR stop*[tiab] OR quit*[tiab] OR reduce*[tiab] OR reduction[tiab] OR relapse*[tiab])
#2	Search (smoking[ti] OR smoker*[ti] OR tobacco[ti] OR nicotine[ti] OR cigar*[ti] OR vape[ti] OR vaping[ti] OR vapour[ti] OR smokeless[ti])
#1	Search "Tobacco Use Disorder"[Mesh:NoExp] OR "Smoking Cessation"[Mesh:NoExp] OR "Tobacco Use Cessation"[Mesh:NoExp] OR "Smoking/prevention and control"[Mesh] OR "Tobacco Use Cessation Products"[Mesh:NoExp] OR "Nicotinic Agonists"[Mesh:NoExp] OR "Tobacco, Smokeless"[Mesh:NoExp] OR "Nicotine Chewing Gum"[Mesh:NoExp] OR "Electronic Nicotine Delivery Systems"[Mesh:NoExp] OR "Smoking Prevention"[Mesh:NoExp]

PsycINFO <1806 to April Week 4 2019>

1 exp Tobacco Smoking/ (29913)
2 exp Smoking Cessation/ (12420)
3 exp Smokeless Tobacco/ (792)
4 exp Electronic Cigarettes/ (909)
5 (smoking or smoker* or tobacco or nicotine or cigar* or vape or vaping or vapour or smokeless).ti. (34380)
6 1 or 2 or 3 or 4 or 5 (39898)
7 limit 6 to "300 adulthood <age 18 yrs and older>" (22887)
8 limit 7 to ("0830 systematic review" or 1200 meta analysis) (95)
9 limit 8 to (english language and yr="2014 -Current") (46)

Literature search strategies for primary literature. Tobacco cessation in adults: Electronic Cigarettes

Sources searched:
Cochrane CDSR Trials, via Wiley
PsycInfo, via Ovid
PubMed
Scopus 2020 and 2019

Key:
* = truncation
ab = word in abstract
id = keyword
kf = keyword heading [word not phrase indexed]
kw = keyword
ti = word in title

Cochrane
Issue 6 of 12, May 2020

#1 (electronic next cigarette*):ti,ab,kw 379
#2 (e next cigarette*):ti,ab,kw 432
#3 "electronic nicotine":ti,ab,kw 157
#4 (e next liquid):ti,ab,kw 57

#5 (vape or vaping):ti,ab,kw 129
#6 (vaporizer* or vapourizer*):ti,ab,kw 2042
#7 (nicotine or tobacco or cigar*):ti,ab,kw 15956
#8 #6 and #7 62
#9 #1 or #2 or #3 or #4 or #5 or #8 with Publication Year from 2013 to 2020, with Cochrane Library publication date Between May 2019 and Dec 2020 193

PsycINFO
Datatabase: APA PsycInfo <1806 to June Week 3 2020>
Search Strategy:
---
1 exp Electronic Cigarettes/ (1332)
2 electronic cigarette*.ti,ab,id. (1097)
3 e-cigarette*.ti,ab,id. (1601)
4 electronic nicotine.ti,ab,id. (215)
5 e-liquid*.ti,ab,id. (114)
6 (vape or vaping).ti,ab,id. (417)
7 (vaporizer* or vapourizer*).ti,ab,id. (64)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2057)
9 limit 8 to (english language and yr="2013 -Current") (1874)
10 (201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020*).up. (191834)
11 9 and 10 (456)

PubMed

(((((((("Electronic Nicotine Delivery Systems"[MeSH Terms:noexp] OR "Vaping"[MeSH Terms:noexp]) OR ((((("e-cigarette"[Title/Abstract] OR "e-cigarettes"[Title/Abstract]) OR "electronic cigarette"[Title/Abstract]) OR "electronic cigarettes"[Title/Abstract]) OR "electronic nicotine"[Title/Abstract])) OR "e-liquid"[Title/Abstract]) OR ("vape"[Title/Abstract] OR "Vaping"[Title/Abstract])) OR (("vaporizer*"[Title/Abstract] OR "vapourizer*"[Title/Abstract]) AND (("nicotine"[Title/Abstract] OR "tobacco"[Title/Abstract]) OR "cigar*"[Title/Abstract]))) NOT ("Animals"[MeSH Terms] NOT ("Animals"[MeSH Terms] AND "Humans"[MeSH Terms]))) AND "English"[Language]) AND 2013/1/1:2020/12/31[Date - Publication]) AND 2019/5/1:2020/6/22[Date - Entry]

Scopus

6 #1 OR #2 OR #3 OR #4 OR #5 AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019)) AND LIMIT-TO (LANGUAGE , "English")

5 (TITLE-ABS-KEY (vaporizer* OR vapourizer*) AND TITLE-ABS-KEY (nicotine OR tobacco OR cigar*))

4 TITLE-ABS-KEY ((vape OR vaping)

3 TITLE-ABS-KEY ("electronic nicotine")

2 TITLE-ABS-KEY ("electronic cigarette*")

1 TITLE-ABS-KEY ("e cigarette*")

Appendix A. Detailed Methods

Literature search strategies for primary literature. Tobacco cessation in adults: Pharmacologic interventions in pregnant women

Sources searched:
Cochrane Central Register of Controlled Clinical Trials, via Wiley
MEDLINE, via Ovid
PsycInfo, via Ovid
PubMed, publisher-supplied

Key:
* = truncation
$ = truncation
ab = word in abstract
exp = explode
id = keyword
kf = keyword heading [word not phrase indexed]
kw = keyword
sb=subset
ti = word in title

COCHRANE
Issue 6 of 12, June 2020

#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 70929
#2 nicotine:ti,ab,kw next replacement*:ti,ab,kw 1741
#3 nicotine:ti,ab,kw near/3 (transdermal or intravenous* or patch* or gum* or spray* or inhaler* or lozenge*):ti,ab,kw 2338
#4 (Nicotrol or Nicoderm or Habitrol or Prostep or Nicorette):ti,ab,kw 131
#5 (Bupropion or Wellbutrin or Zyban or Varenicline or Chantix or Champix):ti,ab,kw 2477
#6 pharm*:ti and (smoking or smoker* or tobacco or nicotine or cigarette*):ti,ab,kw 875
#7 #2 or #3 or #4 or #5 or #6 6091
#8 #1 and #7 with Publication Year from 2014 to 2020, with Cochrane Library publication date Between May 2019 and Dec 2020 34

Medline Non-Indexed
Database: Ovid MEDLINE(R) Epub Ahead of Print <June 19, 2020>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 19, 2020>
Search Strategy:
---
1 Pregnancy/ (0)
2 Pregnant women/ (0)
3 Prenatal care/ (0)
4 Perinatal care/ (0)
5 Postnatal care/ (0)
6 Postpartum period/ (0)

7 Peripartum period/ (0)
8 Maternal Health Services/ (0)
9 Pregnancy complications/ (0)
10 Puerperal Disorders/ (0)
11 pregnan$.ti,ab,kf. (51260)
12 prenatal.ti,ab,kf. (10184)
13 pre natal.ti,ab,kf. (140)
14 perinatal.ti,ab,kf. (7292)
15 peri natal.ti,ab,kf. (25)
16 antenatal.ti,ab,kf. (4824)
17 ante natal.ti,ab,kf. (131)
18 antepartum.ti,ab,kf. (544)
19 ante partum.ti,ab,kf. (75)
20 postnatal.ti,ab,kf. (8795)
21 post natal.ti,ab,kf. (805)
22 postpartum.ti,ab,kf. (6998)
23 post partum.ti,ab,kf. (1365)
24 new mother$.ti,ab,kf. (256)
25 puerperal.ti,ab,kf. (977)
26 or/1-25 (71058)
27 "Tobacco Use Cessation Products"/ (0)
28 Nicotinic Agonists/ (0)
29 Bupropion/ (0)
30 Varenicline/ (0)
31 nicotine replacement$.ti,ab,kf. (445)
32 (nicotine adj3 (transdermal or intravenous$ or patch$ or gum$ or nasal spray$ or inhaler$ or lozenge$)).ti,ab,kf. (230)
33 (Nicotrol or Nicoderm or Habitrol or Prostep or Nicorette).ti,ab,kf. (6)
34 (Bupropion or Wellbutrin).ti,ab,kf. (505)
35 Zyban.ti,ab,kf. (11)
36 Varenicline.ti,ab,kf. (273)
37 Chantix.ti,ab,kf. (11)
38 Champix.ti,ab,kf. (12)
39 pharm$.ti. and (smoking or smoker$ or tobacco or nicotine or cigarette$).ti,ab,kf. (258)
40 stop smoking med$.ti,ab,kf. (10)
41 "Tobacco Use Disorder"/dt or smoking/dt or cigarette smoking/dt or "tobacco use"/dt (0)
42 or/27-41 (1369)
43 26 and 42 (66)
44 Animals/ not (Humans/ and Animals/) (1)
45 43 not 44 (66)
46 limit 45 to (english language and yr="2014 -Current") (47)
47 remove duplicates from 46 (45)

Medline Indexed

Database: Ovid MEDLINE(R) <1946 to June Week 2 2020>, Ovid MEDLINE(R) Daily Update <June 19, 2020>
Search Strategy:

---

1 Pregnancy/ (873141)
2 Pregnant women/ (8225)
3 Prenatal care/ (27513)
4 Perinatal care/ (4574)
5 Postnatal care/ (5607)
6 Postpartum period/ (25355)
7 Peripartum period/ (1159)
8 Maternal Health Services/ (13798)
9 Pregnancy complications/ (90581)
10 Puerperal Disorders/ (11242)
11 pregnan$.ti,ab,kf. (470582)
12 prenatal.ti,ab,kf. (86283)
13 pre natal.ti,ab,kf. (1045)
14 perinatal.ti,ab,kf. (64796)
15 peri natal.ti,ab,kf. (166)
16 antenatal.ti,ab,kf. (30838)
17 ante natal.ti,ab,kf. (424)
18 antepartum.ti,ab,kf. (5276)
19 ante partum.ti,ab,kf. (376)
20 postnatal.ti,ab,kf. (95526)
21 post natal.ti,ab,kf. (6547)
22 postpartum.ti,ab,kf. (47023)
23 post partum.ti,ab,kf. (10555)
24 new mother$.ti,ab,kf. (1505)
25 puerperal.ti,ab,kf. (5840)
26 or/1-25 (1069952)
27 "Tobacco Use Cessation Products"/ (1786)
28 Nicotinic Agonists/ (7272)
29 Bupropion/ (3025)
30 Varenicline/ (1280)
31 nicotine replacement$.ti,ab,kf. (2991)
32 (nicotine adj3 (transdermal or intravenous$ or patch$ or gum$ or nasal spray$ or inhaler$ or lozenge$)).ti,ab,kf. (3118)
33 (Nicotrol or Nicoderm or Habitrol or Prostep or Nicorette).ti,ab,kf. (131)
34 (Bupropion or Wellbutrin).ti,ab,kf. (3824)
35 Zyban.ti,ab,kf. (119)
36 Varenicline.ti,ab,kf. (1480)
37 Chantix.ti,ab,kf. (72)
38 Champix.ti,ab,kf. (43)
39 pharm$.ti. and (smoking or smoker$ or tobacco or nicotine or cigarette$).ti,ab,kf. (2476)
40 stop smoking med$.ti,ab,kf. (45)
41 "Tobacco Use Disorder"/dt or smoking/dt or cigarette smoking/dt or "tobacco use"/dt (1952)
42 or/27-41 (18199)
43 26 and 42 (953)
44 Animals/ not (Humans/ and Animals/) (4675588)

45 43 not 44 (574)
46 limit 45 to (english language and yr="2014 -Current") (181)
47 remove duplicates from 46 (181)
48 Smoking Cessation Agents/ (147)
49 48 not 43 (138)
50 limit 49 to (english language and yr="2014 -Current") (132)
51 50 not 44 (122)
52 (201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020*).ed. (1095231)
53 47 and 52 (39)
54 51 or 53 (161)

PsycInfo
Database: APA PsycInfo <1806 to June Week 3 2020>
Search Strategy:
---
1 exp Pregnancy/ (41840)
2 exp Expectant Mothers/ (710)
3 exp Prenatal Care/ (2070)
4 exp Perinatal Period/ (2836)
5 exp Postnatal Period/ (4650)
6 pregnan*.ti,ab,id. (47446)
7 prenatal.ti,ab,id. (19454)
8 pre natal.ti,ab,id. (251)
9 perinatal.ti,ab,id. (10625)
10 peri natal.ti,ab,id. (66)
11 antenatal.ti,ab,id. (3565)
12 ante natal.ti,ab,id. (57)
13 antepartum.ti,ab,id. (351)
14 ante partum.ti,ab,id. (12)
15 postnatal.ti,ab,id. (20144)
16 post natal.ti,ab,id. (1112)
17 postpartum.ti,ab,id. (12024)
18 post partum.ti,ab,id. (1240)
19 puerperal.ti,ab,id. (509)
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 (96764)
21 exp Tobacco Smoking/ (32427)
22 exp Smoking Cessation/ (13149)
23 exp Smokeless Tobacco/ (850)
24 nicotine.ti,ab,id. (16823)
25 (smoking or smoker* or tobacco or nicotine or cigarette*).ti,ab,id. (69408)
26 21 or 22 or 23 or 24 or 25 (69649)
27 Drug Therapy/ or pharm*.ti. (145315)
28 26 and 27 (3410)
29 exp Bupropion/ (966)
30 nicotine replacement*.ti,ab,id. (1727)
31 (nicotine adj3 (transdermal or intravenous* or patch* or gum* or nasal spray* or inhaler* or lozenge*)).ti,ab,id. (1789)
32 (nicotrol or nicoderm or habitrol or prostep or nicorette).ti,ab,id. (48)

33 (bupropion or wellbutrin).ti,ab,id. (2178)
34 zyban.ti,ab,id. (44)
35 varenicline.ti,ab,id. (832)
36 chantix.ti,ab,id. (43)
37 champix.ti,ab,id. (17)
38 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (7581)
39 20 and 38 (247)
40 limit 39 to (english language and yr="2014 -Current") (82)
41 (201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020*).up. (191834)
42 40 and 41 (10)

PubMed, publisher-supplied records

((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]) AND (("nicotine replacement"[tiab]) OR (nicotine[tiab] AND (transdermal[tiab] OR intravenous*[tiab] OR patch*[tiab] OR gum[tiab] OR gums[tiab] OR spray*[tiab] OR inhaler*[tiab] OR lozenge*[tiab])) OR (nicotra[tiab] OR nikodem[tiab] OR habitual[tiab] OR prostej[tiab] OR Nicorette[tiab]) OR (Bupropion[tiab] OR Wellbutrin[tiab] OR Zyban[tiab] OR Varenicline[tiab] OR Chantix[tiab] OR Champix[tiab]) OR (pharm*[ti] AND (smoking[tiab] OR smoker*[tiab] OR tobacco[tiab] OR nicotine[tiab] OR cigarette*[tiab])))) AND publisher[sb] Filters: from 2014 – 2020 [21 results]

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Include	Exclude
Aim	Tobacco cessation in adults who currently use tobacco, regardless of readiness to quit, including relapse prevention	• Primary prevention of tobacco use • Tobacco harm–reduction strategies
Condition	Current use of any tobacco product, including but not limited to: cigarettes, e-cigarettes and other electronic nicotine delivery systems (ENDS), cigars, cigarillos and filtered cigars, smokeless tobacco (including snus pouches), pipe tobacco, 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 who currently use tobacco	Reviews limited to: • Children and adolescents • Persons with other comorbid health conditions (e.g., chronic obstructive pulmonary disease, cardiovascular conditions, cancer, HIV)
Interventions	Primary care–relevant tobacco cessation interventions that can be provided in primary care or are feasible to refer to from primary care, including pharmacotherapy, behavioral interventions, and e-cigarettes or ENDS, alone or in combination.	Broad public health initiatives (e.g., mass media, communitywide campaigns)
Setting	Any setting applicable to primary care, including interventions that take place in settings that can be referred to from primary care	Reviews limited to studies that take place in worksites, churches, or other settings where participants have existing social connections
Comparators	• No intervention • Usual care • Waitlist • Attention control (e.g., intervention is similar in format and intensity but on a different content area) • Minimal intervention (no more than a single brief contact [i.e., <5 minutes] per year, brief written materials, such as pamphlets, or self-help materials) • 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) • Maternal and perinatal morbidity/mortality • Dental/oral health • Quality of life *Other outcomes:* • Health care utilization **KQ 2 (behavioral outcomes):** Tobacco cessation/tobacco abstinence (continuous or point prevalence abstinence) **KQ 3 (harms):** Serious treatment-related harms at any time point after the intervention began	Reviews that only report: • Reduction in smoking/tobacco (based on frequency/quantity only) • Reduction in withdrawal symptoms • Attitudes, knowledge, or beliefs related to tobacco use • Intentions to change behavior • Intervention participation/compliance

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Include	Exclude
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 or start of intervention
Study design	*Pharmacotherapy and behavioral interventions in adults and behavioral interventions in pregnant women (review-of-reviews):* **All KQs:** 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. *Pharmacotherapy in pregnant women; e-cigarette or ENDS interventions* **All KQs:** Randomized and nonrandomized controlled trials **KQ 3:** The above, plus observational cohort studies (n≥1,000)	
Study geography	Reviews and primary studies that primarily take place in countries categorized as "Very High" on the Human Development Index (as defined by the United Nations Development Programme)	Reviews in which >50% of included studies take place in countries not categorized as "Very High" on the Human Development Index
Publication language	English	Any language other than English
Quality rating	Fair- or good-quality studies	Poor-quality studies

Appendix A Table 2. Study-Design Quality Rating Criteria

Study Design	Adapted Quality Criteria
Cohort studies*, adapted from Newcastle-Ottawa Scale[212]	**Bias arising in randomization process or due to confounding** • Balance in baseline characteristics • No baseline confounding • No time-varying confounding **Bias in selecting participants into the study** • No evidence of biased selection of sample • Start of followup and start of intervention coincide **Bias due to departures form intended interventions** • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias in classifying interventions** • Fidelity to intervention protocol • Participants were analyzed as originally allocated **Bias from missing data** • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** No evidence that the measures, analyses, or subgroup analyses are selectively reported
Randomized clinical trials*, adapted from U.S. Preventive Services Task Force Manual[74]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated

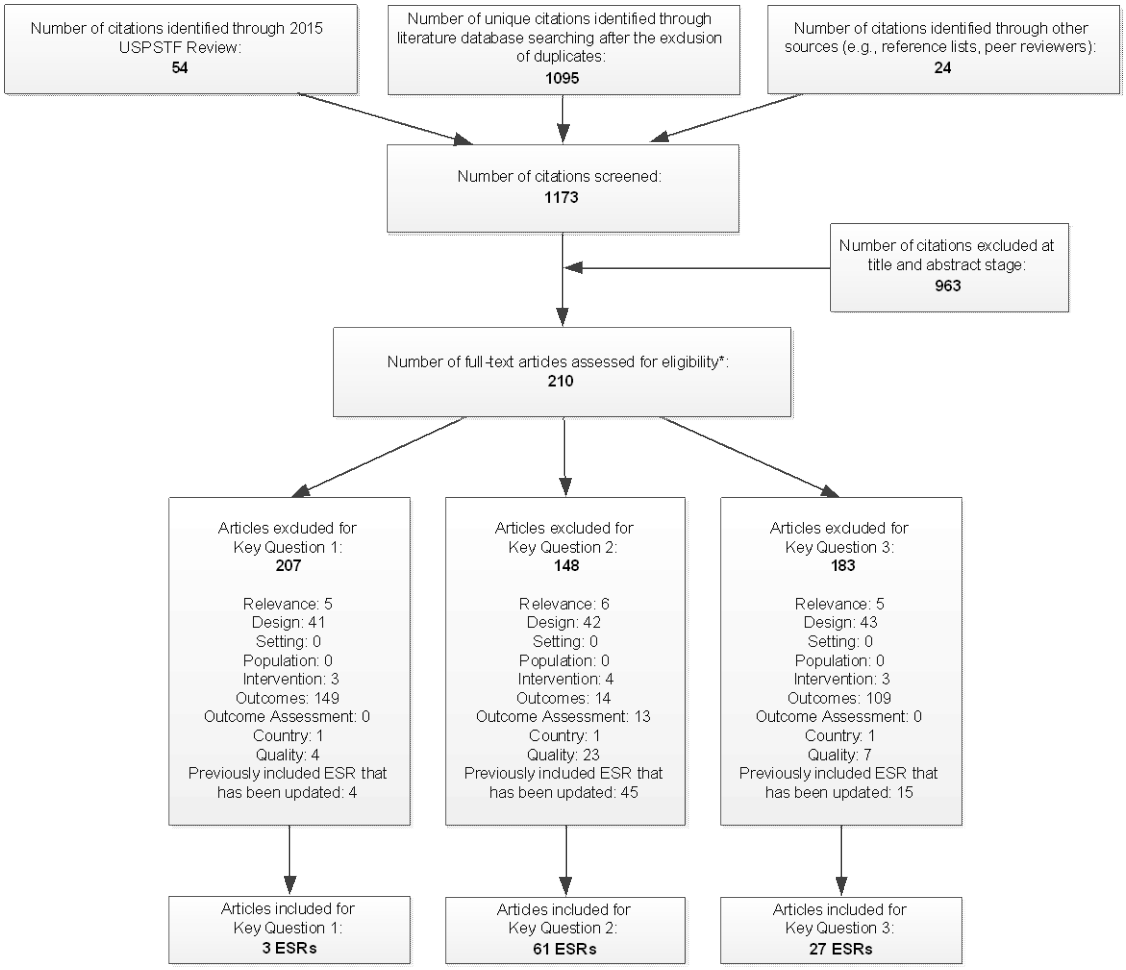
Appendix A Table 2. Study-Design Quality Rating Criteria

Study Design	Adapted Quality Criteria
	Bias from missing data • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** No evidence that the measures, analyses, or subgroup analyses are selectively reported
Systematic review†, AMSTAR 2[73]	• Research questions and inclusion criteria for the review included components of PICO • Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and the report justified any significant deviations from the protocol • The selection of the study designs for inclusion in the review was explained • A comprehensive literature search strategy was used • Study selection was performed in duplicate • Data extraction in was performed duplicate • A list of excluded studies and justifications for the exclusions were provided • The included studies were described in adequate detail • A satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review was used • Sources of funding for the studies included were reported • If meta-analysis was performed, appropriate methods for statistical combination of results were performed • If meta-analysis was performed, the potential impact of RoB in the individual studies on the results on the MA or other evidence synthesis were assessed. • RoB in individual studies were accounted for when interpreting/discussing the results of the review • A satisfactory explanation for, and discussion of, any heterogeneity observed itn the results to the review was provided • If a quantitative synthesis was performed, an adequate investigation of publication bias (small study bias) was performed and its likely impact on the results of the review was discussed • Any potential sources of conflict of interest, included any funding authors received for conducting the review was reported

* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer.

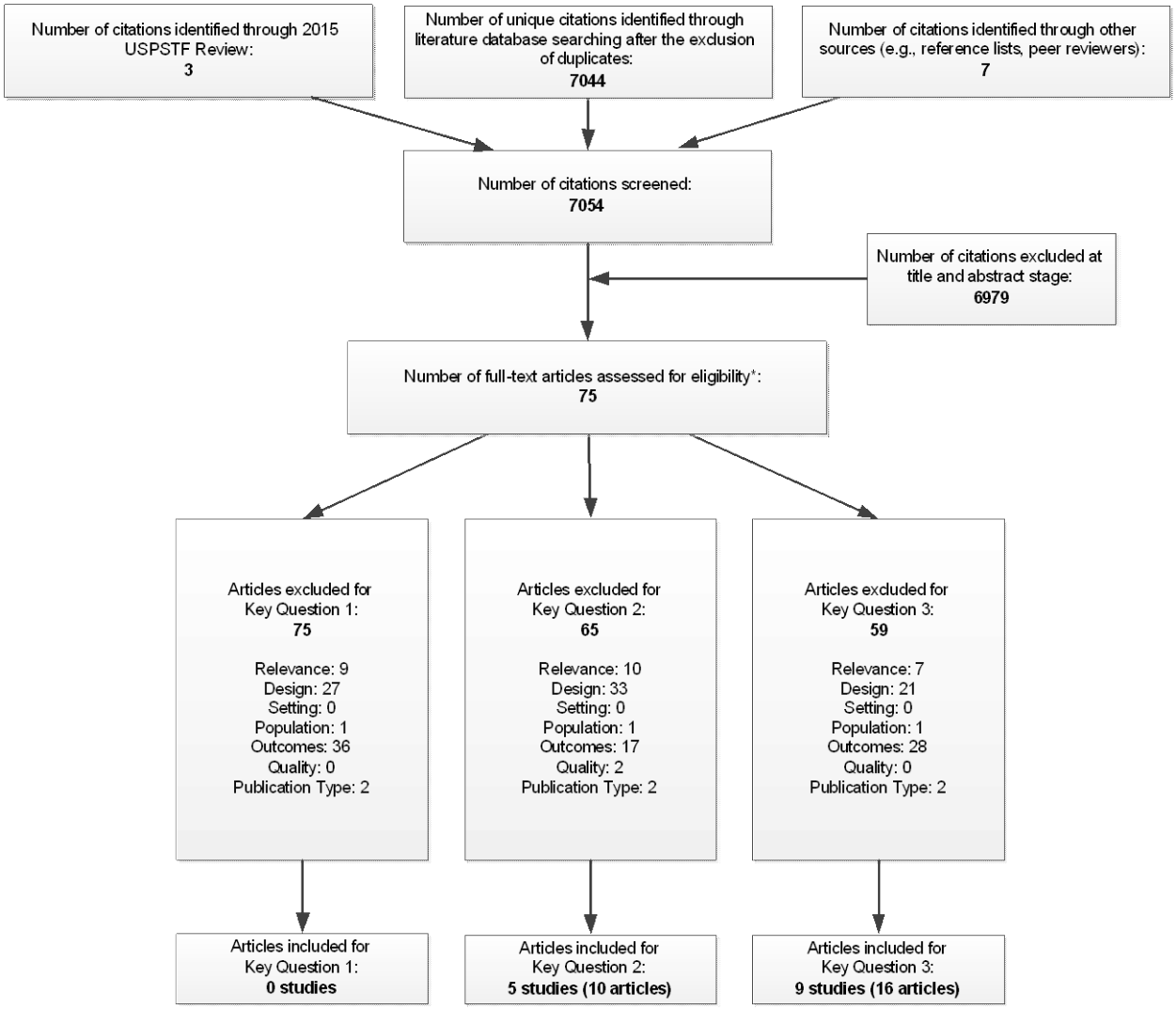
† Overall confidence in the results of each review was rated according to published guidance: a rating of "high" reflects that the review had zero or one noncritical weakness; "moderate" indicates the review was judged to have more than one noncritical weakness; "low" means the review was judged to have one critical flaw with or without noncritical weaknesses or multiple noncritical weaknesses; and "critically low" signifies that more than one critical flaw was present.

Appendix B Figure 1. Literature Flow Diagram, Tobacco Cessation in Adults: Overview of Reviews



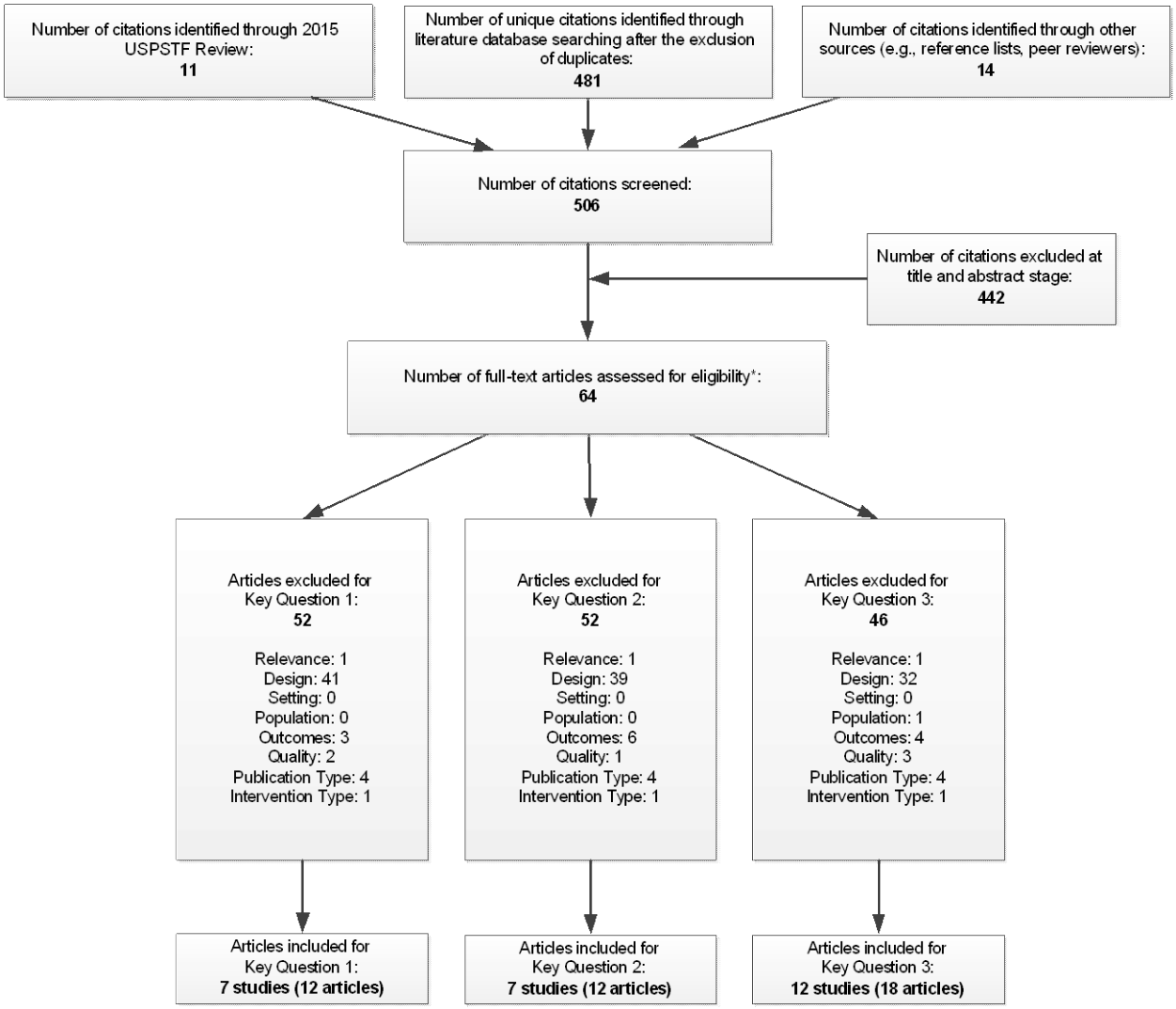
* Articles may appear under more than one Key Question
Abbreviations: ESRs = existing systematic reviews

Appendix B Figure 2. Literature Flow Diagram, Tobacco Cessation in Adults: Electronic Cigarettes



* Articles may appear under more than one Key Question

Appendix B Figure 3. Literature Flow Diagram, Tobacco Cessation in Adults: Pharmacotherapy Interventions Among Pregnant Women



* Articles may appear under more than one Key Question

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Agboola, 2015[79]	Sept-2013	Adult smokers	Varenicline	Varenicline	NR	Smoking abstinence	NR	≥3 months	RCTs
Ahmed, 2018[80]	July-2018	Smokers with schizophrenia, schizophreniform, schizoaffective, or delusional disorder	Varenicline	Varenicline	Placebo	Smoking abstinence, AEs	NR	NR	RCTs
Appolonio, 2016[81]	Aug-2016	Adult smokers aged 15 years or older with alcohol or other drug dependence	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention	Usual tobacco cessation therapies provided in alcohol and drug treatment; delayed treatment; lower treatment level; no tobacco-related cessation therapy	Smoking abstinence	Inpatient or outpatient treatment	Any followup	RCTs
Boland, 2016[83]	May-2016	Smokers (excluding smokeless tobacco or e-cig users) of any age, of low-socioeconomic status, disadvantaged groups (e.g. homeless persons, Indigenous and native persons, prisoners, at-risk-youth, persons with a mental	Mobile phone- or internet-based support	Technology-based intervention, including those delivered via mobile phone or internet	NR	Smoking abstinence	NR	Any followup	RCTs or quasi-RCTs

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
		illness, persons using substances or diagnosed with a substance use disorder, persons with a disability or chronic illness such as HIV-positive persons), including pregnant women							
Carson, 2012[86]	April-2011	Indigenous smokers of any age	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention	Usual care, minimal or no intervention, placebo	Smoking abstinence	Any	≥6 months	RCTs or quasi-RCTs
Danielsson, 2014[89]	May-2013	Adult smokers, excluding pregnant persons	Telephone- or internet-based support	Telephone or web-based interventions, focused on pure telephone or internet-based self-help	NR	Smoking abstinence	NR	≥3 months	RCTs or quasi-RCTs
Denison, 2017[90]	Nov-2016	Adults smokers	Cognitive therapy	Cognitive therapies promoting smoking cessation	No intervention; usual care; other behavioral intervention	Smoking abstinence; physiological or clinical outcomes related to smoking	NR	NR	RCTs or systematic reviews
Do, 2018[91]	Mar-2017	Smokers of any age, excluding smokeless tobacco users	eHealth smoking cessation intervention	Web-based intervention, computer-generated programs, mobile-based	Usual practice or other smoking cessation methods	Smoking abstinence	NR	≥1 month	RCTs, quasi-RCTs, interrupted time series, and

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
				interventions, and other electronic platforms					controlled before-after
Ebbert, 2015[92]	June-2015	Users of any age of any tobacco product that is placed in the mouth and not burned	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention	Placebo; less intensive intervention; usual care	Smoking abstinence	NR	≥6 months	RCTs or quasi-RCTs
Giles, 2014[93]	Apr-2012	Non-clinical, adult (at least 50% of the sample aged 18 years or above) populations, living in high-income economies	Financial-based incentives	Financial incentives: cash, cash-like rewards, or penalties contingent on behavior change	Usual care; no intervention	Smoking abstinence	NR	≥6 months	RCTs
Graham, 2016[94]	Apr-2015	Adult smokers	Internet-based interventions	Internet-based interventions	NR	Smoking abstinence	NR	≥1 month	RCTs
Griffiths, 2018[186]	May-2017	Pregnant smokers aged 16 years and older	Digital interventions	Any intervention delivered through computer, video or DVD, mobile phone or handheld device	Usual care; other intervention	Smoking abstinence	NR	End of pregnancy	RCTs or quasi-RCTs
Johnston, 2013[99]	May-2012	Nonindigenous and indigenous smokers of any age from Australia, New Zealand, United States, or Canada	Any tobacco cessation intervention	Any tailored or nontailored pharmacologic, behavioral, or combination tobacco cessation intervention	Nontailored tobacco control intervention or usual care	Smoking abstinence	NR	NR	RCTs, CCTs

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Khanna, 2016[100]	Apr-2015	Smokers aged 18 to 65 years and suffering from serious mental illness (e.g. schizophrenia, schizophrenia-like disorders, bipolar disorder, serious affective disorders)	Advice	Tobacco cessation advice, defined as "preventive information or counsel that leaves the recipient to make the final decision".	Usual care	Smoking abstinence; AEs; quality of life; smoking cessation awareness	NR	Any followup	RCTs
Kishi, 2014[101]	Aug-2014	Smokers of any age, including pregnant women, with schizophrenia, schizoaffective disorder, schizophreniform disorder, or delusional disorder	Varenicline (Harms only)	Varenicline	Placebo	AEs	NR	≥8 weeks	RCTs
Klinsophon, 2017[102]	Nov-2016	Smokers of any age who wished to quit or who were recent quitters, excluding pregnant persons	Exercise	Exercise alone or as an adjunct program to smoking cessation	Any control, including another smoking cessation intervention that did not include exercise	Smoking abstinence	NR	≥6 months	RCTs
Lindson-Hawley, 2015[213]	Aug-2014	Adult tobacco users, excluding pregnant persons	Motivational interviewing	Behavioral intervention using motivational interviewing	Brief advice; low-intensity intervention; routine care	Smoking abstinence	NR	≥6 months	RCTs

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Liu, 2013[107]	Apr-2013	Children and adults of African-, Chinese- or South Asian-origin	Adapted interventions for ethnic minorities	Adapted behavioral tobacco cessation interventions for ethnic minorities	Usual care or nonadapted intervention	Smoking abstinence	Any	NR	Any
McCabb. 2019[111]	Sept-2018	Adult smokers, excluding pregnant persons and smokeless tobacco users	Internet-based interventions	Internet-based intervention with or without additional support such as medication or other behavioral support	No treatment or other smoking cessation intervention	Smoking abstinence	Any	Any	RCTs
McKee, 2016[112]	Dec-2014	Tobacco users of any age	Varenicline	Varenicline	Placebo	Smoking abstinence	NR	≥3 months	RCTs
Notley, 2019[116]	July-2018	Pregnant smokers	Incentives	Incentive schemes, lotteries, raffles, and contingent or non-contingent payments, to reward cessation and abstinence in smoking cessation programs	Usual care, other smoking cessation intervention without incentives, another incentive-based intervention differing by incentive type or amount	Smoking abstinence, AEs	Any	End of pregnancy	RCTs
Palmer, 2018[117]	Jan-2016	Smokers of any age	Mobile phone-based support	Mobile phone-based support	NR	Smoking abstinence	NR	Any followup	RCTs
Peckham, 2017[118]	Sept-2016	Adults smokers with severe mental illness	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention or	Placebo; comparative effectiveness; usual care; no intervention	Smoking abstinence; AEs; change in psychiatric symptoms; change in	Either in-patient or outpatient settings	Any followup	RCTs

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
				the use of e-cigarettes as a smoking cessation aid		body weight			
Roberts, 2016[120]	Dec-2014	Adult smokers with severe mental illness motivated to attempt to quit or reduce smoking	NRT, bupropion, varenicline	NRT, bupropion, varenicline	Placebo; alternative pharm	Smoking abstinence; AEs	NR	≥6 months	RCTs
Rosen, 2018[121]	Dec-11, July-12, July-13 (used 3 Cochrane reviews)	Adult smokers, excluding pregnant persons	NRT, bupropion, varenicline	NRT, bupropion, varenicline	No active medication	Smoking abstinence	NR	6 months and 12 months	RCTs
Schuit, 2018[122]	Aug-2016	Adult smokers	NRT, bupropion, varenicline	NRT, bupropion, varenicline	Placebo; usual care; alternative pharm; non-pharm intervention; no-intervention control; different doses or durations of pharm; different NRT formats; combinations of pharm; different types or intensities of behavioral support as adjunct to pharm	Smoking abstinence	Any	Any followup	RCTs or quasi-RCTs

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
Schwartz, 2015[123]	Feb-2014	Smokeless tobacco users of any age	Varenicline	Varenicline	Placebo	Smoking abstinence; AEs	NR	12 weeks; 6 months	RCTs
Smith, 2016[124]	Dec-2015	Adult smokers	NRT, bupropion, varenicline	NRT, bupropion, varenicline	Placebo	Smoking abstinence	NR	≥6 months	RCTs
Thurgood, 2016[132]	Aug-2014	Adult smokers in substance abuse treatment or recovery	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention	Placebo; usual care	Smoking abstinence	NR	≥6 months	RCTs
Tsoi, 2013[133]	Oct-2012	Adult smokers with schizophrenia or schizoaffective disorder	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention	Another intervention, placebo or usual care	Smoking abstinence; AEs; change in mental state	NR	≥6 months	RCTs or quasi-RCTs
van der Meer, 2013[136]	Apr-2013	Adult smokers with current or past depression	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention	Usual care or placebo	Smoking abstinence	Any	≥6 months	RCTs
Wilson, 2017[139]	Jan-2017	Smokers in selected disadvantaged groups (e.g. homeless, prisoners, indigenous populations, at-risk youth, people on low income, those with mental	Any behavioral support	Any behavioral tobacco cessation intervention	Another behavioral intervention; usual care	Smoking abstinence	Only studies conducted in full OECD countries (US, Canada, Australia, New Zealand,	≥3 months	RCTs

Appendix C Table 1. Inclusion Criteria of Ancillary Systematic Reviews on the Effectiveness and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Last search date	Population	Specific Intervention	Intervention criteria	Comparison	Outcomes	Setting	Followup	Study design
		illness)					United Kingdom, and Western Europe)		
Wilson, 2018[187]	July-2017	Pregnant smokers of any age	Psychotherapy or incentive-based interventions	Psychotherapy delivered in at least 2 sessions or incentives to be earned contingent on abstinence	Usual care or any smoking cessation intervention not including incentives	Smoking abstinence	NR	≥3 months	RCTs
Windle, 2016[140]	July-2015	Cigarette smokers of any age motivated to quit	NRT, bupropion, varenicline	NRT, bupropion, varenicline	Placebo or alternative pharm	Smoking abstinence; AEs; SAEs	NR	≥12 months	RCTs
Wu, 2015[141]	Apr-2015	Adults smokers not motivated to quit	Any tobacco cessation intervention	Any pharmacologic, behavioral, or combination tobacco cessation intervention	Placebo; no intervention; other behavioral support except for reduction support	Smoking abstinence; AEs	NR	≥6 months	RCTs
Wu, 2016[142]	Sept-2015	Adult smokers with a severe mental illness	Varenicline (Harms only)	Varenicline	Placebo; alternative pharm	Psychiatric AEs	In- and out-patient settings in any country	NR	RCTs or quasi-RCT

Abbreviations: AE = Adverse event; CCT = Controlled clinical trial; NR = Not reported; NRT = Nicotine replacement therapy; OECD = Organization for Economic Cooperation and Development; RCT = Randomized controlled trial; SAE = Serious adverse event

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
Agboola, 2015[79]	Varenicline	19	32 - 1210	39 - 57	NR	All trials used a regimen of 0.5 mg for the first week of treatment followed by 1-mg tablets of varenicline administered twice daily for a n additional 11 weeks except three; one in which varenicline was administered for 7 weeks, another in which participants received varenicline for 52 weeks, and a third study in which varenicline was administered for an additional 12 weeks as maintenance treatment following a 12 week treatment period. All trials provided brief support (behavioral counseling delivered face-to-face or via telephone) throughout the treatment phase, except one study in which participants received a personalized quit message and a printed information sheet at baseline only. All trials continued brief counseling during the non-treatment follow-up phase, either face-to-face or via telephone, except two studies in which participants received a quit message at baseline only and supplies of varenicline at follow-up visits and access to quitlne counseling during the treatment phase only. Only two studies documented the use of specific relapse prevention counseling indicating that, in most of the included studies, relapse prevention may not have been a major feature of support provided.	NR	NR
Ahmed, 2018[80]	Varenicline	4	9 – 127	41 – 42	NR	Varenicline treatment for 12 weeks	NR	NR
Appolonio, 2016[81]	Any tobacco cessation intervention	34	36 - 575	NR	NR	Counseling (k=11) included one-time or multi-session individual counseling or motivational interviewing sessions, cognitive behavioral therapy, and group counseling sessions. Pharmacotherapy (k=11) included naltrexone or topiramate, nicotine gum, nicotine patches + gum, bupropion, and varenicline. Combination therapy (k=12) included combined counseling and pharmacotherapy (NRT or bupropion) versus usual care.	Inpatient and outpatient	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
Boland, 2016[83]	Mobile phone- or internet-based support	13	100 - 2142	22 - 47.4	Average, 16.9 (range NR)	Websites to deliver cessation support targeted at low-income smokers and HIV positive smokers (k=5) Computer program to deliver cessation advice and support to substance dependent smokers, smokers with a mental illness, and predominantly African American pregnant smokers (k=5) 60-minute culturally specific cessation DVD for African American smokers (k=1) Integrated video-telephony for rural low-SES smokers (k=1) Mobile phone text-message cessation support for Indigenous smokers (k=1) Tailored intervention and study materials to respective disadvantaged group with the aim of reducing health inequalities (k=9)	NR	NR
Carson, 2012[86]	Any tobacco cessation intervention	4	111 - 601	24.5 - 39.9	NR	Intervention durations ranged from seven weeks to six months. One study had two days of training for doctors and clinical staff with no data provided on intervention duration received by patients.	Remote locations; health clinics	NR
Danielsson, 2014[89]	Telephone- or internet-based support	74	38 - 73,000	20.1 - 57.4	NR	Internet intervention vs. control (k=21) Helpline intervention vs. control (k=12) Remaining studies focused on alcohol use or gambling	NR	NR
Denison, 2017[90]	Cognitive therapy	21	25 - 677	21 - 60	NR	Most interventions included one or more of the following cognitive or cognitive-behavioral content, in order of frequency: relapse prevention, coping skills, self-management, self-efficacy, social support, cognitive restructuring, problem solving, motivational interview, stress management, and rearrangement of environment-per- son interaction. One study evaluated interventions based on an acceptance and commitment approach, and one study focused on environment-person interactions. Most studies used individual counselling.	NR	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
Do, 2018[91]	eHealth smoking cessation intervention	108	2 – 23,213	NR	NR	Majority of studies used web-based programs followed by wireless and mobile phone-based programs, and computer-assisted interventions. Few studies investigated social media, virtual chat rooms, or other electronic aids.	NR	NR
Ebbert, 2015[92]	Any tobacco cessation intervention	34	42 - 2523	17 - 44	Two studies reported the average number of dips per day, ranging from 7.9 to 11 dips per day at baseline. One study only enrolled participants consuming 3 cans or pouches of smokeless tobacco per week. All other studies required participants to be current ST users at enrollment.	Pharmacologic: Bupropion SR was sustained release; NRT included patches, lozenges, and gum. In all cases, both the treatment and control groups received the same behavioral interventions. Behavioral: stratified on the basis of whether the intervention targeted individuals or organizations and included oral screening, counseling (telephone or group (peer-led or nursing-led)), mailings, posters, videos, in-person feedback, manuals, informational websites, and quitlines.	Any setting, including dental offices, community settings, school, military	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
Giles, 2014[93]	Financial-based incentives	8	141 - 11,281	NR	NR	Most interventions offered cash rewards and/or vouchers exchangeable for a specific range of goods or services; two studies used deposit contracts where participants made cash deposits at the start of the intervention which were only returned in the event of successful behavior change - resulting in potential financial penalties. Two studies also included additional uncertain rewards contingent on behavior change in addition to certain rewards. The total value of incentives, over and above any payments for study participants, ranged from $5.16 to $786 (in 2011 US$). Intervention periods ranged from two weeks to 24 months.	NR	NR
Graham, 2016[94]	Internet-based interventions	40	122 - 23,213	19.8 - 49.5	NR	Static web interventions: Ten trials included stand-alone static web components as part of the intervention condition. Static content was generally informational and non-tailored and contained content comparable to a printed cessation guide. Included in this category are static interventions in which the intervention is fully available and those that deliver intervention components over time. In some studies, static content was paired with additional features such as tailored feedback reports, text messaging, and/or social support. Tailored feedback: Tailored feedback consists of advice or information provided to users based on responses to one or more assessments. Eight studies examined interventions consisting largely of a feedback report. Tailoring was often performed on the basis of participants' responses to an initial assessment and/or on the basis of participants' stage of quitting. The form of tailored messages, however, varied greatly. In one study, participants could receive up to 150 tailored emails over 6–12 months with tailoring on multiple factors. In contrast, another study provided participants with	Varied	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
						a single tailored letter, six to nine pages in length, based on a 62-item questionnaire. Interactive/tailored web intervention: The majority of studies evaluated the effectiveness of interactive web interventions. Interactivity was defined as any part of a web intervention that solicited/required user input and included features such as exercises, quizzes, cost calculators, tailored messages, quit planning tools, training in coping strategies, and self-monitoring. A minority of the interactive interventions offered tailored content and/or guided users through the intervention based on information provided by the participant. Coaching analogs and social support: A number of trials included social support resources such as peers, coaches, or counselors. The most common form of social support was the provision of an asynchronous discussion forum. Eight trials included a discussion forum, either moderated by a peer or an expert, in at least some of the study arms. Seven trials included access to live coaching or counseling either via telephone, face-to-face counseling, or SMS text or email. Two studies evaluated other methods of accessing social support. Other adjunctive components: Four trials described the use of SMS text messaging as part of the intervention. Two trials also included interactive voice response calls. Two other studies included an online eight module cognitive-behavioral mood management component in some arms. Another study included videos and the ability to create video content. Medication: Several studies provided pharmacotherapy along with the web-based intervention. Nicotine replacement therapy (NRT) was the most common form of pharmacotherapy and was included in seven trials. Medication		

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
						treatment ranged from a 2-week starter kit used in one study to a 10-week starter kit used in another study. Two trials included 12 weeks of varenicline. One study included a 9-week course of bupropion.		
Griffiths, 2018[186]	Digital interventions	12	17 – 918	23 – 30.5	NR	Four studies delivered digital content through text messages. Three studies used videotapes, and one study used telephone Interactive Voice Response Technology (IVR). Two trials used websites, including a contingency management program, and an interactive and personalized website. The remaining two trials were computer programs.	Home, clinical setting	NR
Johnston, 2013[99]	Any tobacco cessation intervention	5	226 - 1705	NR	NR	Three studies were pragmatic trials that recruited participants through New Zealand's Quitline service with the aim of testing the effectiveness of enhanced protocols, specifically (a) precessation nicotine replacement therapy (NRT), (b) familiarization and choice of NRT product, and (c) very low nicotine content cigarettes (VLNC) compared with usual care. The other two studies trialed a smoking cessation counseling intervention using mobile phone technology.	Recruited from Quitline service (k=3)	NR
Khanna, 2016[100]	Advice	0	NA	NA	NA	NA	NA	NA
Kishi, 2015[101]	Varenicline (Harms only)	7	9 - 128	39.9 - 51.4	NR	All trials provided varenicline at 1-2mg/day plus psychotherapy	Outpatient	NR
Klinsophon, 2017[102]	Exercise	19	20 - 2318	NR	NR	Details of interventions not synthesized. Aerobic exercise (k=14) Resistance training (k=1) Yoga (k=1) Combined aerobic and resistance exercise program (k=1) Did not specify the precise type of exercise and were classified as "physical activity" (k=2) Supervised, group-based exercise at the research setting plus home-based exercise (k=8) Supervised, group-based exercise at the	NR	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
						research setting (k=7) Home-based exercise (k=3) Remaining provided home-based exercise or supervised, group-based exercise in each group		
Liu, 2013[107]	Adapted interventions for ethnic minorities	28	NR	NR	NR	Most interventions were adapted for African American smokers (k=23) and the remaining were adapted for Chinese Americans (k=5). The most frequency used adaptations were to develop materials specifically for the target population, followed by the use of materials that reflected the target population's reading and literacy level, material that depicted individuals from the target population, appropriate graphics and scenarios, and intervention content that targeted the population's social and cultural values.	NR	Physicians, lay health educators, lay counselors, neighborhood health advocates, nurses
McCrabb, 2019[111]	Internet-based interventions	45	35-16,430	20-50	NR	Internet-based interventions with or without additional interventions components such as phone calls, medication, group support.	NR	NR
McKee, 2016[112]	Varenicline	16	79 - 703	NR	NR	Majority of studies delivered 1mg bid. Varenicline duration was mostly 12 weeks (14/16 trial) with 1 study at 6weeks and 1 lasting 52wks. Study duration ranged from 24 to 52; majority 52 wks (9/16 trials) while 7 were 24 or 26wks in duration.	Hospitalized adults (k=1)	NR
Notley, 2019*[116]	Incentives	10	17-1014	24-30.7	NR	Largest trial provided cash payments as the incentive. In all other cases the rewards were vouchers for goods or services. All the trials offered a program of practical cessation support, in addition to usual care.	Antenatal programs, substance misuse treatment clinics	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
Palmer, 2018[117]	Mobile phone-based support	18	31 - 5800	19 - 43	NR	Twelve interventions were delivered by SMS, three were delivered by voice calls, one by interactive voice response, one by a combination of SMS and video messages, and one by a mobile application with voice calls.	Recruited from internet, quitline, lung cancer screening, local newspaper, cancer network membership, mail, emergency department, electronic health record, and phone recruitment	NR
Peckham, 2017[118]	Any tobacco cessation intervention	26	5 - 298	NR	NR	The varenicline studies all followed a standard dosing schedule whereas the dose in the Bupropion SR studies ranged from 150 mg once per day to 150 mg twice per day. Smoking cessation counselling, whether part of the intervention being tested or part of the control arm, consisted of a range of behavior change techniques delivered in a variety of formats e.g. face-to-face one-to-one sessions, face-to-face group sessions or one-to-one sessions delivered via telephone. It is important to note that in the trials of varenicline and bupropion, where smoking cessation counselling was delivered, the same program was delivered in both the medication (varenicline or bupropion) arm of the trial as in the usual care arm of the trial. In the majority of the trials the exact content, in terms of the behavior change techniques employed in the smoking cessation counselling, was insufficiently described.	Outpatients (k=20), inpatient (k=1)	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
Roberts, 2016[120]	NRT, bupropion, varenicline	14	5 - 128	NR	NR	Number of CBT sessions varied by study	NR	NR
Rosen, 2018[121]	NRT, bupropion, varenicline	61	36 - 3575	NR	NR	For comparators: "Some studies included more than two treatment groups. For 2 × 2 factorial designs that included a medical and a non-medical (behavioral/ psychological) intervention, two separate comparisons were performed: one for the active non-medical intervention and one for the inactive non-medical intervention. In cases where high- and low- dependent smoker subgroups were randomized separately to intervention and control arms, each subgroup was treated in the meta-analysis as a separate study. In studies with multiple doses and a single control, participants assigned any non-zero dose were combined into a single intervention group. For trials with multiple intervention arms which did not have a clear 2 × 2 design, we compared the two groups that were identical on all aspects of the intervention except for provision of medication.	NR	NR
Schuit, 2017[122]	NRT, bupropion, varenicline	18	61 - 1686	41 - 46	NR	NRT vs. placebo (k=4) Bupropion SR vs. placebo (k=6) NRT vs. bupropion SR vs. NRT + Bupropion SR (k=1) NRT vs. varenicline (k=1) Bupropion SR vs. NRT + Bupropion SR (k=1) Basic support + NRT vs. weekly support + NRT (k=1) No intervention vs. extended NRT vs. extended NRT + CBT vs. extended NRT vs. extended counselling (k=1) NRT, patch vs. NRT, nasal spray with group counseling provided to all participants (k=1) NRT oral dose (tailored by DNA analysis) vs. NRT oral dose (tailored by nicotine dependence questionnaire) (k=1)	Community and healthcare	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
						Varenicline + telephone counselling vs. varenicline + web intervention vs. varenicline + telephone counselling + web intervention (k=1)		
Schwartz, 2016[123]	Varenicline	3	76 - 431	34.2 - 43.9	NR	All trials included behavioral counseling (details not specified) 2 trials assessed at both timepoints: Varenicline at a dose of 0.5mg once daily on Days 1–3, increased to 0.5mg twice daily on Days 4–7, and further increased to a target dose of 1mg twice daily for 11 weeks; for a total of 12 weeks of treatment. The 3rd trial with only 12wk FU: Varenicline at a dose of 0.5mg once daily on Days 1–3, increased to 0.5mg twice daily on Days 4–7, and further increased to a target dose of 1mg once daily for 11 weeks in participants weighing <55kg, and a target dose of 1mg twice daily in participants weighing ≥55kg; for a total of 12 weeks of treatment.	NR	NR
Smith, 2016[124]	NRT, bupropion, varenicline	28	56 - 842	NR	NR	All NRT trials included transdermal nicotine patches ranging from 14mg to 42mg per day for 6 to 18 weeks with varying levels of counseling. All Bupropion SR trials provided 150mg 2/day for 6 to 10 weeks with varying levels of counseling. Varenicline doses ranges from 0.3 mg 1/day to 1mg 2/day for 12 weeks with varying levels of counseling.	Primary care (k=4), community volunteers (k=26), smoking cessation clinic (k=2), community health center (k=1)	NR
Thurgood, 2016[132]	Any tobacco cessation intervention	17	64 - 383	34 - 50	16 - 32	The main intervention categories included counseling only; counseling and NRT; NRT only; CBT only; CBT and NRT; motivational interviewing; contingency management; bupropion; and varenicline.	Inpatient substance abuse treatment (k=4) 21-day	Masters and doctoral level clinicians, trained therapists, counselors,

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
							inpatient alcohol detox (k=1) Outpatient substance abuse treatment (k=1) Outpatient methadone treatment (k=1)	graduate students, psychologists trained in CBT, research physicians, first author provided counseling, interventionists
Tsoi, 2013[133]	Any tobacco cessation intervention	34	9 - 298	34 - 48.7	7 – 41	The duration of drug treatment varied from 7 hours to 6 months.	"Most trials recruited participants from the community"; inpatient units, the community, or outpatient psychiatric treatment sites	NR
van der Meer, 2013[136]	Any tobacco cessation intervention	49	14 - 5046	24 - 57	7.9 – 32.3	In most trials, the psychosocial mood management component of the experimental intervention consisted of a format of (cognitive) behavioral therapy for depression. In one trial the psychosocial mood management component consisted of a cognitive behavioral analysis system of psychotherapy, in one trial of hypnosis skills, and in one trial of exercise counselling. The interventions of all of four of Muñoz's trials had a self-help format, one trial had a group counselling format, two trials had an individual counselling format, two trials had an individual plus telephone counselling format, one trial had a telephone counselling format, one had a telephone	Trials conducted in community, university, and clinical settings including hospitals	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
						counselling plus self-help format, and one had a group plus self-help format. All trials except the four conducted by Muñoz had interventions with multi-session behavioral support. Seven trials had time-matched comparisons. Three trials had additional pharmacotherapy in both arms, and six trials had no additional pharmacotherapy in both arms.		
Wilson, 2017[139]	Any behavioral support	24	30 - 4613	21.9 - 54.8	NR	NRT (k=9), Bupropion SR (k=2), nortriptyline (k=1), behavioral therapy varied, included motivational interviewing, smoking cessation counselling, group therapy, CBT, weekly classes, financial incentives, exercise, computer-delivered programs, phone counselling, contingency management, motivational enhancement, and educational videos	Community or health centers	NR
Wilson, 2018[187]	Incentives	22	54 – 941	23 – 31	Mean: 10	Sixteen trials provided psychotherapy to smokers with total session time ranging from 50 min to 480 min over 2 or more sessions. Six trials provided incentive-based interventions ranging from a maximum of $250 to $1180 contingent upon abstinence.	Public prenatal clinic, WIC clinic, community, prenatal clinic, HMO, army medical center, women's hospital, MIC clinic, maternity hospital, addiction program	NR

Appendix C Table 2. Descriptive Characteristics of Included Studies Within the Ancillary Reviews on the Efficacy and Adverse Events of Tobacco Cessation Interventions Among Adults, by Author

Author, Year	Intervention	Total # of included studies	Sample size (range)	Average age (range)	Average CPD at BL (range)	Intervention description	Setting	Providers
Windle, 2016[140]	NRT, bupropion, varenicline	123	51 - 3684	16 - 63	7 - 38	NRT patch + BT vs. BT (k=15) Short-acting NRT + BT vs. BT (k=29) NRT + BT vs. BT (k=44) Bupropion SR + BT vs. BT (k=20) Varenicline + BT vs. BT (k=14) Nicotine patch + BT vs. Nicotine Patch (k=4) NRT + BT vs. NRT (k=6) Pharmacotherapy + BT vs. Pharmacotherapy (k=7) Pharmacotherapy + Intensive BT vs. Pharmacotherapy + Minimal BT (k=5) Pharmacotherapy combinations NRT + NRT vs. NRT monotherapy (k=7) Nicotine patch + Short-acting NRT vs. Nicotine Patch (k=5) Bupropion SR + NRT vs. Monotherapy (k=4) Pharmacotherapy + Pharmacotherapy vs. Pharmacotherapy (k=12)	NR	NR
Wu, 2015[141]	Any tobacco cessation intervention	14	67 - 1410	38.5 - 55.4	NR	Reduction support + medication vs. reduction support + placebo (k=9) Reduction support + medication vs.no intervention (k=5) Reduction support + medication vs. reduction support vs.no intervention (k=1)	NR	NR
Wu, 2016[142]	Varenicline (Harms only)	8	5 - 127	NR	NR	The selected randomized trials all compared varenicline with placebo. Three studies explored the effectiveness of varenicline alone, and the remaining studies evaluated varenicline in combination with individual behavioral interventions. The duration of the varenicline treatment varied between 8 and 12 weeks; 81% of participants treated with varenicline completed the treatment, compared with 82% in placebo groups.	NR	NR

*Evidence for pregnant persons only

Abbreviations: bid = Two times a day; BL = Baseline; BT = Behavioral therapy; CBT = Cognitive behavioral therapy; CPD = Cigarettes per day; DNA = Deoxyribonucleic acid; DVD = Digital versatile disc; FU = Followup; HIV = Human immunodeficiency virus; kg = kilogram; mg = milligram; NA = Not applicable; NR = Not reported; NRT = Nicotine replacement therapy; SES = Socioeconomic status; SMS = Short message service; ST = Smokeless tobacco; wks = weeks; US = United States; VLNC = Very low nicotine content cigarettes

Appendix D List 1. Included ESRs, by Author

Ancillary publication(s) indented under primary article

Agboola SA, Coleman T, McNeill A, et al. Abstinence and relapse among smokers who use varenicline in a quit attempt-a pooled analysis of randomized controlled trials. *Addiction*. 2015;110(7):1182-93. PMID: 25846123. https://doi.org/10.1111/add.12941

Ahmed S, Virani S, Kotapati VP, et al. Efficacy and safety of varenicline for smoking cessation in schizophrenia: a meta-analysis. *Front Psychiatry*. 2018;9:428. PMID: 30283363. https://doi.org/10.3389/fpsyt.2018.00428

Apollonio D, Philipps R, Bero L. Interventions for tobacco use cessation in people in treatment for or recovery from substance use disorders. *Cochrane Database Syst Rev*. 2016;11:CD010274. PMID: 27878808. https://doi.org/10.1002/14651858.CD010274.pub2

Barnes J, McRobbie H, Dong CY, et al. Hypnotherapy for smoking cessation. *Cochrane Database Syst Rev*. 2019;6:CD001008. PMID: 31198991. https://doi.org/10.1002/14651858.CD001008.pub3

Boland VC, Stockings EA, Mattick RP, et al. The methodological quality and effectiveness of technology-based smoking cessation interventions for disadvantaged groups: a systematic review and meta-analysis. *Nicotine Tob Res*. 2018;20(3):276-285. PMID: 28034998. https://doi.org/10.1093/ntr/ntw391

Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. *Cochrane Database Syst Rev*. 2014;12:CD008743. PMID: 25547090. https://doi.org/10.1002/14651858.CD008743.pub3

Cahill K, Lindson-Hawley N, Thomas KH, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016;5:CD006103. PMID: 27158893. https://doi.org/10.1002/14651858.CD006103.pub7

Carson K, V, Brinn MP, Peters M, et al. Interventions for smoking cessation in Indigenous populations. *Cochrane Database Syst Rev*. 2012;1:CD009046 PMID: 22258998. https://doi.org/10.1002/14651858.CD009046.pub2

Chamberlain C, O'Mara-Eves A, Porter J, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev*. 2017;2:CD001055. PMID: 28196405. https://doi.org/10.1002/14651858.CD001055.pub5

Chang PH, Chiang CH, Ho WC, et al. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689. PMID: 26198192. https://doi.org/10.1186/s12889-015-2055-0

Clair C, Mueller Y, Livingstone-Banks J, et al. Biomedical risk assessment as an aid for smoking cessation. *Cochrane Database Syst Rev*. 2019;3:CD004705. PMID: 30912847. https://doi.org/10.1002/14651858.CD004705.pub5

Danielsson AK, Eriksson AK, Allebeck P. Technology-based support via telephone or web: a systematic review of the effects on smoking, alcohol use and gambling. *Addict Behav*. 2014;39(12):1846-68. PMID: 25128637. https://doi.org/10.1016/j.addbeh.2014.06.007

Appendix D List 1. Included ESRs, by Author

Denison E, Underland V, Mosdol A, et al. Cognitive Therapies for Smoking Cessation: A Systematic Review. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2017.

Do HP, Tran BX, Le Pham Q, et al. Which eHealth interventions are most effective for smoking cessation? A systematic review. *Patient Pref Adherence*. 2018;12:2065-84. PMID: 30349201. https://doi.org/10.2147/ppa.S169397

Ebbert JO, Elrashidi MY, Stead LF. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev*. 2015;10:CD004306. PMID: 26501380. https://doi.org/10.1002/14651858.CD004306.pub5

Giles E, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis (Structured abstract). *Plos One*. 2014;9(3):e90347. PMID: 24618584. https://doi.org/10.1371/journal.pone.0090347

Graham AL, Carpenter KM, Cha S, et al. Systematic review and meta-analysis of Internet interventions for smoking cessation among adults. *Subst Abuse Rehabil*. 2016;7:55-69. PMID: 27274333. https://doi.org/10.2147/sar.s101660

Griffiths SE, Parsons J, Naughton F, et al. Are digital interventions for smoking cessation in pregnancy effective? A systematic review and meta-analysis. *Health Psychol Rev*. 2018;12(4):333-56. PMID: 29912621. https://doi.org/10.1080/17437199.2018.1488602

Hartmann-Boyce J, Chepkin SC, Ye W, et al. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018;5:CD000146. PMID: 29852054. https://doi.org/10.1002/14651858.CD000146.pub5

Hartmann-Boyce J, Hong B, Livingstone-Banks J, et al. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev*. 2019;6:CD009670. PMID: 31166007. https://doi.org/10.1002/14651858.CD009670.pub4

Hollands GJ, Naughton F, Farley A, et al. Interventions to increase adherence to medications for tobacco dependence. *Cochrane Database Syst Rev*. 2019;8:CD009164. PMID: 31425618. https://doi.org/10.1002/14651858.CD009164.pub3

Howes S, Hartmann-Boyce J, Livingstone-Banks J, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2020;4:CD000031. PMID: 32319681. https://doi.org/10.1002/14651858.CD000031.pub5

Johnston V, Westphal DW, Glover M, et al. Reducing smoking among indigenous populations: new evidence from a review of trials. *Nicotine Tob Res*. 2013;15(8):1329-38. PMID: 23519776. https://doi.org/10.1093/ntr/ntt022/

Khanna P, Clifton AV, Banks D, et al. Smoking cessation advice for people with serious mental illness. *Cochrane Database Syst Rev*. 2016;1:CD009704. PMID: 26816385. https://doi.org/10.1002/14651858.CD009704.pub2

Kishi T, Iwata N. Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2015;265(3):259-68. PMID: 25283510. https://doi.org/10.1007/s00406-014-0551-3

Klinsophon T, Thaveeratitham P, Sitthipornvorakul E, et al. Effect of exercise type on smoking cessation: a meta-analysis of randomized controlled trials. *BMC Res Notes*. 2017;10(1):442. PMID: 28874175. https://doi.org/10.1186/s13104-017-2762-y

Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev*. 2017;3:CD001292. PMID: 28361496. https://doi.org/10.1002/14651858.CD001292.pub3

Lindson N, Chepkin S, Ye W, et al. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2019;4:CD013308. https://doi.org/10.1002/14651858.CD013308

Lindson N, Klemperer E, Hong B, et al. Smoking reduction interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019;9:CD013183. PMID: 31565800. https://doi.org/10.1002/14651858.CD013183.pub2

Lindson N, Thompson TP, Ferrey A, et al. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*. 2019;7:CD006936. PMID: 31425622. https://doi.org/10.1002/14651858.CD006936.pub4

Liu JJ, Wabnitz C, Davidson E, et al. Smoking cessation interventions for ethnic minority groups: a systematic review of adapted interventions. *Prev Med*. 2013;57(6):765-75. PMID: 24076130.

Livingstone-Banks J, Norris E, Hartmann-Boyce J, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019;2:CD003999. PMID: 30758045. https://doi.org/10.1002/14651858.CD003999.pub5

Livingstone-Banks J, Ordonez-Mena JM, Hartmann-Boyce J. Print-based self-help interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019;1:CD001118. PMID: 30623970. https://doi.org/10.1002/14651858.CD001118.pub4

Matkin W, Ordonez-Mena JM, Hartmann-Boyce J. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev*. 2019;5:CD002850. PMID: 31045250. https://doi.org/10.1002/14651858.CD002850.pub4

McCrabb S, Baker AL, Attia J, et al. Internet-based programs incorporating behavior change techniques are associated with increased smoking cessation in the general population: a systematic review and meta-analysis. *Ann Behav Med*. 2019;53(2):180-95. PMID: 29750240. https://doi.org/10.1093/abm/kay026

McKee SA, Smith PH, Kaufman M, et al. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. *Nicotine Tob Res*. 2016;18(5):1002-11. PMID: 26446070. https://doi.org/10.1093/ntr/ntv207

Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation*. 2014;129(1):28-41. PMID: 24323793. https://doi.org/10.1161/CIRCULATIONAHA.113.003961

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. https://doi.org/10.1186/1617-9625-8-8

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Appendix D List 1. Included ESRs, by Author

Moyo F, Archibald E, Slyer JT. Effectiveness of decision aids for smoking cessation in adults: a quantitative systematic review. *JBI Database System Rev Implement Rep*. 2018;16(9):1791-822. PMID: 30204670. https://doi.org/10.11124/jbisrir-2017-003698

Notley C, Gentry S, Livingstone-Banks J, et al. Incentives for smoking cessation. *Cochrane Database Syst Rev*. 2019;7:CD004307. PMID: 31313293. https://doi.org/10.1002/14651858.CD004307.pub6

Palmer M, Sutherland J, Barnard S, et al. The effectiveness of smoking cessation, physical activity/diet and alcohol reduction interventions delivered by mobile phones for the prevention of non-communicable diseases: a systematic review of randomised controlled trials. *PLoS One*. 2018;13(1):e0189801. PMID: 29304148. https://doi.org/10.1371/journal.pone.0189801

Peckham E, Brabyn S, Cook L, et al. Smoking cessation in severe mental ill health: what works? an updated systematic review and meta-analysis. *BMC Psychiatry*. 2017;17(1):252. PMID: 28705244. https://doi.org/10.1186/s12888-017-1419-7

Rice VH, Heath L, Livingstone-Banks J, et al. Nursing interventions for smoking cessation. *Cochrane Database Syst Rev*. 2017;12:CD001188. PMID: 29243221. https://doi.org/10.1002/14651858.CD001188.pub5

Roberts E, Evins A, McNeill A, et al. Efficacy and tolerability of pharmacotherapy for smoking cessation in adults with serious mental illness: a systematic review and network meta-analysis. *Addiction*. 2016;111(4):599-612. PMID: 26594837. http://dx.doi.org/10.1111/add.13236

Rosen LJ, Galili T, Kott J, et al. Diminishing benefit of smoking cessation medications during the first year: a meta-analysis of randomized controlled trials. *Addiction*. 2018;113(5):805-16. PMID: 29377409. https://doi.org/10.1111/add.14134

Schuit E, Panagiotou OA, Munafo MR, et al. Pharmacotherapy for smoking cessation: effects by subgroup defined by genetically informed biomarkers. *Cochrane Database Syst Rev*. 2017;9:CD011823. PMID: 28884473. https://doi.org/10.1002/14651858.CD011823.pub2

> Panagiotou OA, Schuit E, Munafo MR, et al. Smoking cessation pharmacotherapy based on genetically-informed biomarkers: what is the evidence? *Nicotine Tob Res*. 2019;21(9):1289-1293. PMID: 30690475. https://doi.org/10.1093/ntr/ntz009

Schwartz J, Fadahunsi O, Hingorani R, et al. Use of varenicline in smokeless tobacco cessation: a systematic review and meta-analysis. *Nicotine Tob Res*. 2016;18(1):10-6. PMID: 25646351. https://doi.org/10.1093/ntr/ntv010

Smith PH, Weinberger AH, Zhang J, et al. Sex differences in smoking cessation pharmacotherapy comparative efficacy: a network meta-analysis. *Nicotine Tob Res*. 2016;[Epub ahead of print]. https://doi.org/10.1093/ntr/ntw144

Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. *Cochrane Database Syst Rev*. 2013;5:CD000165. PMID: 23728631. https://doi.org/10.1002/14651858.CD000165.pub4

Stead LF, Carroll AJ, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database Syst Rev*. 2017;3:CD001007. PMID: 28361497. https://doi.org/10.1002/14651858.CD001007.pub3

Stead LF, Koilpillai P, Fanshawe TR, et al. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2016;3:CD008286. PMID: 27009521. https://doi.org/10.1002/14651858.CD008286.pub3

Sterling LH, Windle SB, Filion KB, et al. Varenicline and adverse cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2016;5(2):e002849. PMID: 26903004. https://doi.org/10.1161/jaha.115.002849

Taylor GMJ, Dalili MN, Semwal M, et al. Internet-based interventions for smoking cessation. *Cochrane Database Syst Rev*. 2017;9:CD007078. PMID: 28869775. https://doi.org/10.1002/14651858.CD007078.pub5

Thomas D, Abramson MJ, Bonevski B, et al. System change interventions for smoking cessation. *Cochrane Database Syst Rev*. 2017;2:CD010742. PMID: 28185257. https://doi.org/10.1002/14651858.CD010742.pub2

Thomas KH, Martin RM, Knipe DW, et al. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. *BMJ*. 2015;350:h1109. PMID: 25767129.

Thurgood SL, McNeill A, Clark-Carter D, et al. A systematic review of smoking cessation interventions for adults in substance abuse treatment or recovery. *Nicotine Tob Res*. 2016;18(5):993-1001. PMID: 26069036. http://dx.doi.org/10.1093/ntr/ntv127

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. https://doi.org/10.1002/14651858.CD007253.pub3

Tzelepis F, Paul CL, Williams CM, et al. Real-time video counselling for smoking cessation. *Cochrane Database Syst Rev*. 2019;2019;10:CD012659. PMID: 31684699. https://doi.org/10.1002/14651858.CD012659.pub2

Ussher MH, Faulkner GEJ, Angus K, et al. Exercise interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019;2019;10:CD002295. PMID: 31684691. https://doi.org/10.1002/14651858.CD002295.pub6

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. https://doi.org/10.1002/14651858.CD006102.pub2

White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. *Cochrane Database Syst Rev*. 2014;1:CD000009. PMID: 24459016. https://doi.org/10.1002/14651858.CD000009.pub4

Whittaker R, McRobbie H, Bullen C, et al. Mobile phone text messaging and app-based interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019;10:CD006611. PMID: 31638271. https://doi.org/10.1002/14651858.CD006611.pub5

Wilson A, Guillaumier A, George J, et al. A systematic narrative review of the effectiveness of behavioural smoking cessation interventions in selected disadvantaged groups (2010-2017). *Expert Rev Respir Med*. 2017;11(8):617-30. PMID: 28608758. https://doi.org/10.1080/17476348.2017.1340836

Wilson SM, Newins AR, Medenblik AM, et al. Contingency management versus psychotherapy for prenatal smoking cessation: a meta-analysis of randomized controlled trials. *Womens Health*. 2018;28(6):514-23. PMID: 30061033. https://doi.org/10.1016/j.whi.2018.05.002

Windle SB, Filion KB, Mancini JG, et al. Combination therapies for smoking cessation: a hierarchical Bayesian meta-analysis. *Am J Prev Med*. 2016;51(6):1060-71. PMID: 27617367. https://doi.org/10.1016/j.amepre.2016.07.011

Wu L, Sun S, He Y, et al. Effect of smoking reduction therapy on smoking cessation for smokers without an intention to quit: an updated systematic review and meta-analysis of randomized controlled. *Int J Environ Res Public Health*. 2015;12(9):10235-53. PMID: 26308034. https://doi.org/10.3390/ijerph120910235

Wu Q, Gilbody S, Peckham E, et al. Varenicline for smoking cessation and reduction in people with severe mental illnesses: systematic review and meta-analysis. *Addiction*. 2016;111(9):1554-67. PMID: 27043328. https://doi.org/10.1111/add.13415

Ancillary publication(s) indented under primary article

Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382(9905):1629-37. PMID: 24029165. https://doi.org/10.1016/S0140-6736(13)61842-5

Bullen C, Howe C, Laugesen M. Electronic cigarettes for smoking cessation: a randomised controlled trial. *J Vasc Surg*. 2014;59(3):872. PMID: 24029165 https://doi.org/10.1016/j.jvs.2014.01.028

Bullen C, Williman J, Howe C, et al. Study protocol for a randomised controlled trial of electronic cigarettes versus nicotine patch for smoking cessation. *BMC Public Health*. 2013;13:210. PMID: 23496861. https://doi.org/10.1186/1471-2458-13-210

O'Brien B, Knight-West O, Walker N, et al. E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. *Tob Induc Dis.* 2015;13(1):5. PMID: 25814920. https://doi.org/10.1186/s12971-015-0030-2

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. https://doi.org/10.1371/journal.pone.0066317

Caponnetto P, Campagna D, Cibella F, et al. Erratum: EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*. 2014;9(1). https://doi.org/10.1371/annotation/e12c22d3-a42b-455d-9100-6c7ee45d58d0

Carpenter MJ, Heckman BW, Wahlquist AE, et al. A naturalistic, randomized pilot trial of e-cigarettes: uptake, exposure, and behavioral effects. *Cancer Epidemiol Biomarkers Prev*. 2017;26(12):1795-803. PMID: 29127080. https://doi.org/10.1158/1055-9965.epi-17-0460

Cravo AS, Bush J, Sharma G, et al. A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. *Regul Toxicol Pharmacol*. 2016;81(Suppl 1):S1-S14. PMID: 27769828. https://doi.org/10.1016/j.yrtph.2016.10.003

Hajek P, Phillips-Waller A, Przulji D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380:629-37. PMID: 30699054. https://doi.org/10.1056/NEJMoa1808779

Hajek P, Phillips-Waller A, Przulj D, et al. E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: the TEC RCT. *Health Technol Assess*. 2019;23(43):1-82. PMID: 31434605. https://dx.doi.org/10.3310/hta23430

Lee SH, Ahn SH, Cheong YS. Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: a randomized controlled study. *J Am Board Fam Med*. 2019;32(4):567-74. PMID: 31300577. https://doi.org/10.3122/jabfm.2019.04.180384

Masiero M, Lucchiari C, Mazzocco K, et al. E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: preliminary results by randomized controlled trial. *Nicotine Tob Res*. 2018;21(1):119-26. PMID: 29660034. https://doi.org/10.1093/ntr/nty047

Masiero M, Lucchiari C, Mazzocco K, et al. Corrigendum: E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: preliminary results by randomized controlled trial. *Nicotine Tob Res*. 2020;22(4):594-5. https://doi.org/10.1093/ntr/nty175

Lucchiari C, Masiero M, Veronesi G, et al. Benefits of e-cigarettes among heavy smokers undergoing a lung cancer screening program: randomized controlled trial protocol. *JMIR Res Protocols*. 2016;5(1):e21. PMID: 26842790. https://doi.org/10.2196/resprot.4805

Tseng TY, Ostroff JS, Campo A, et al. A randomized trial comparing the effect of nicotine versus placebo electronic cigarettes on smoking reduction among young adult smokers. *Nicotine Tob Res*. 2016;18(10):1937-43. PMID: 26783292. https://doi.org/10.1093/ntr/ntw017

Walker N, Parag V, Verbiest M, et al. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respir Med*. 2019;[Epub ahead of print]. PMID: 31515173. https://doi.org/10.1016/S2213-2600(19)30269-3

Appendix D List 3. Included Studies for Pharmacotherapy Interventions Among Pregnant Women, by Author

Ancillary publication(s) indented under primary article

Berard A, Zhao JP, Sheehy O. Success of smoking cessation interventions during pregnancy. *Am J Obstet Gynecol*. 2016;215(5):611.e1-.e8. PMID: 27402053. https://dx.doi.org/10.1016/j.ajog.2016.06.059

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.

Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. *New Engl J Med*. 2012;366(9):808-18. PMID: 22375972.

Cooper S, Lewis S, Thornton JG, et al. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy--clinical effectiveness and safety until 2 years after delivery, with economic evaluation. *Health Technol Assess*. 2014;18(54):1-128. PMID: 25158081. https://dx.doi.org/10.3310/hta18540

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. *Lancet Respir Med*. 2014(9):728-37. PMID: 25127405.

Essex HN, Parrott S, Wu Q, et al. Cost-effectiveness of nicotine patches for smoking cessation in pregnancy: a placebo randomized controlled trial (SNAP). *Nicotine Tob Res*. 2015;17(6):636-42. PMID: 25481916. https://dx.doi.org/10.1093/ntr/ntu258

Iyen B, Vaz LR, Taggar J, et al. Is the apparently protective effect of maternal nicotine replacement therapy (NRT) used in pregnancy on infant development explained by smoking cessation? Secondary analyses of a randomised controlled trial. *BMJ Open*. 2019;9(7):e024923. PMID: 31300493. https://dx.doi.org/10.1136/bmjopen-2018-024923

Vaz LR, Coleman T, Cooper S, et al. The nicotine metabolite ratio in pregnancy measured by trans-3'-hydroxycotinine to cotinine ratio: characteristics and relationship with smoking cessation. *Nicotine Tob Res*. 2015;17(11):1318-23. PMID: 25589677. https://dx.doi.org/10.1093/ntr/ntu342

Dhalwani NN, Szatkowski L, Coleman T, et al. Stillbirth among women prescribed nicotine replacement therapy in pregnancy: analysis of a large UK pregnancy cohort. *Nicotine Tob Res*. 2019;21(4):409-415. PMID: 29394405. https://doi.org/10.1093/ntr/nty019

Dhalwani NN, Szatkowski L, Coleman T, et al. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. *Pediatrics*. 2015;135(5):859-67. PMID: 25847803. http://dx.doi.org/10.1542/peds.2014-2560

El-Mohandes AA, Windsor R, Tan S, et al. A randomized clinical trial of trans-dermal nicotine replacement in pregnant African-American smokers. *Matern Child Health J*. 2013;17(5):897-906. PMID: 22761006.

Oncken C, Dornelas E, Greene J, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. *Obstet Gynecol*. 2008;112(4):859-67. PMID: 18827129. https://doi.org/10.1097/AOG.0b013e318187e1ec

Appendix D List 3. Included Studies for Pharmacotherapy Interventions Among Pregnant Women, by Author

Oncken C, Dornelas EA, Kuo CL, et al. Randomized trial of nicotine inhaler for pregnant smokers. *Am J Obstet Gynecol MFM*. 2019;1(1):10-8. PMID: 31380506. https://doi.org/10.1016/j.ajogmf.2019.03.006

Pedersen L, Petronis KR, Norgaard M, et al. Risk of adverse birth outcomes after maternal varenicline use: a population-based observational study in Denmark and Sweden. *Pharmacoepidemiol Drug Saf*. 2020;29(1):94-102. PMID: 31713302. https://dx.doi.org/10.1002/pds.4894

Pollak KI, Oncken CA, Lipkus IM, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. *Am J Prev Med*. 2007;33(4):297-305. PMID: 17888856. https://doi.org/10.1016/j.amepre.2007.05.006

Tran DT, Preen DB, Einarsdottir K, et al. Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study. *BMC Med*. 2020;18(1):15. PMID: 32019533. https://dx.doi.org/10.1186/s12916-019-1472-9

Wisborg K, Henriksen TB, Jespersen LB, et al. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstet Gynecol*. 2000;96(6):967-71. PMID: 11084187. https://doi.org/10.1016/s0029-7844(00)01071-1

Zhu JL, Olsen J, Liew Z, et al. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. *Pediatrics*. 2014;134(2):e382-8. PMID: 25049343. https://dx.doi.org/10.1542/peds.2014-0213

Appendix E List 2. Excluded Studies List, Tobacco Cessation in Adults: Electronic Cigarettes

Exclusion Code	Definition
E1	ESR 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	ESR among pharmacotherapy interventions among pregnant women (not included study design)
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
E9	Review published in language other than English
E10	Previous Review: Primary ESR that has been updated
E11	Previous Review: Non-primary ESR that will not move forward
E12	Poor Quality

1. [No authors listed]. Cardiac adverse effects of nicotine replacement therapy. *Prescrire Int*. 2015;24(166):292-3. PMID: 26788573. **KQ1E2a, KQ2E2a, KQ3E2a.**

2. Afshin A, Babalola D, McLean M, et al. Information technology and lifestyle: a systematic evaluation of internet and mobile interventions for improving diet, physical activity, obesity, tobacco, and alcohol use. *J Am Heart Assoc*. 2016;5(9):e003058. PMID: 27581172. https://doi.org/10.1161/jaha.115.003058 **KQ1E6, KQ2E12, KQ3E6.**

3. Aldi GA, Bertoli G, Ferraro F, et al. Effectiveness of pharmacological or psychological interventions for smoking cessation in smokers with major depression or depressive symptoms: a systematic review of the literature. *Subst Abus.* 2018;39(3):289-306. PMID: 29436984. https://doi.org/10.1080/08897077.2018.1439802 **KQ1E6, KQ2E12, KQ3E12.**

4. Ali A, Kaplan CM, Derefinko KJ, et al. Smoking cessation for smokers not ready to quit: meta-analysis and cost-effectiveness analysis. *Am J Prev Med*. 2018;55(2):253-62. PMID: 29903568. 10.1016/j.amepre.2018.04.021 **KQ1E6, KQ2E12, KQ3E6.**

5. Aubin HJ, Luquiens A, Berlin I. Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. *Br J Clin Pharmacol*. 2014;77(2):324-36. PMID: 23488726. https://dx.doi.org/10.1111/bcp.12116 **KQ1E2a, KQ2E2a, KQ3E2a.**

6. Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? *Addiction*. 2010;105(7):1176-89. PMID: 20491721. **KQ1E11, KQ2E11, KQ3E11.**

7. Bar-Zeev Y, Bonevski B, Lim LL, et al. Improving health providers smoking cessation care in pregnancy: a systematic review and meta-analysis. *Addict Behav*. 2019;93:29-38. PMID: 30684819.

10.1016/j.addbeh.2019.01.002 **KQ1E6, KQ2E1, KQ3E6.**

8. Barnes J, Dong CY, McRobbie H, et al. Hypnotherapy for smoking cessation. *Cochrane Database Syst Rev*. 2010;10:CD001008. PMID: 20927723. **KQ1E6, KQ2E10, KQ3E10.**

9. Barry K, Finke J. Nicotine replacement therapy for tobacco cessation. 2020;102(1):17-18. *Am Fam Physician*. **KQ1E2a, KQ2E2a, KQ3E2a**

10. Berger I, Mooney-Somers J. Smoking cessation programs for lesbian, gay, bisexual, transgender, and intersex people: a content-based systematic review. *Nicotine Tob Res*. 2017;19(12):1408-17. PMID: 27613909. https://doi.org/10.1093/ntr/ntw216 **KQ1E6, KQ2E7, KQ3E6.**

11. Bize R, Burnand B, Mueller Y, et al. Biomedical risk assessment as an aid for smoking cessation. *Cochrane Database Syst Rev*. 2012;12:CD004705. PMID: 23235615. **KQ1E6, KQ2E10, KQ3E6.**

12. Bodner ME, Dean E. Advice as a smoking cessation strategy: a systematic review and implications for physical therapists. *Physiother Theory Pract*. 2009;25(5-6):369-407. PMID: 19842864. **KQ1E6, KQ2E11, KQ3E6.**

13. Brose LS, Simonavicius E, McNeill A. Maintaining abstinence from smoking after a period of enforced abstinence - systematic review, meta-analysis and analysis of behaviour change techniques with a focus on mental health. *Psychol Med*. 2018;48(4):669-678. PMID: 28780913. https://doi.org/10.1017/s0033291717002021 **KQ1E1, KQ2E1, KQ3E1.**

14. 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;10(3):150-62. PMID: 23421669. **KQ1E6, KQ2E11, KQ3E6.**

15. Brown TJ, Hardeman W, Bauld L, et al. A systematic review of behaviour change techniques within interventions to prevent return to smoking postpartum. *Addict Behav*. 2019;92:236-43. PMID: 30731328. 10.1016/j.addbeh.2018.12.031 **KQ1E6, KQ2E12, KQ3E6.**

16. Bull ER, McCleary N, Li X, et al. Interventions to promote healthy eating, physical activity and smoking in low-income groups: a systematic review with meta-analysis of behavior change techniques and delivery/context. *Int J Behav Med*. 2018;25(6):605-16. PMID: 30003476. 10.1007/s12529-018-9734-z **KQ1E1, KQ2E1, KQ3E1.**

17. Bush T, Lovejoy JC, Deprey M, et al. The effect of tobacco cessation on weight gain, obesity, and diabetes risk. *Obesity*. 2016;24(9):1834-41. PMID: 27569117. 10.1002/oby.21582 **KQ1E2a, KQ2E2a, KQ3E2a.**

18. Cahill K, Hartmann-Boyce J, Perera R. Incentives for smoking cessation. *Cochrane Database Syst Rev*. 2015;5:CD004307. PMID: 25983287. https://doi.org/10.1002/14651858.CD004307.pub5 **KQ1E6, KQ2E10, KQ3E10.**

19. Cahill K, Lancaster T, Green N. Stage-based interventions for smoking cessation. *Cochrane Database Sys Rev*. 2010;11:CD004492. PMID: 21069681. **KQ1E6, KQ2E11, KQ3E6.**

20. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2012;4:CD006103. PMID: 22513936. **KQ1E6, KQ2E10, KQ3E10.**

21. Canadian Agency for Drugs and Technologies in Health. Nicotine Replacement Therapy for Smoking Cessation or Reduction: A Review of the Clinical Evidence. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2014. PMID: 24741730. **KQ1E2a, KQ2E2a, KQ3E2a.**

22. Canadian Agency for Drugs and Technologies in Health. Smoking Cessation Aids for Patients in Treatment for Substance Abuse: Clinical Effectiveness, Cost-Effectiveness and Guidelines. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2015. **KQ1E2a, KQ2E2a, KQ3E2a.**

23. Canadian Agency for Drugs and Technologies in Health. Telehealth Delivery of Group Smoking Cessation Programs for Adolescents and Young Adults: Clinical Effectiveness. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2015. **KQ1E2a, KQ2E2a, KQ3E2a.**

24. Canadian Agency for Drugs and Technologies in Health. Nicotine Replacement Therapy, Bupropion and Varenicline for Tobacco Cessation: A Review of Clinical Effectiveness. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2016. **KQ1E2a, KQ2E2a, KQ3E2a.**

25. Canadian Agency for Drugs and Technologies in Health. Smoking Cessation Interventions for Patients With Severe Mental Illnesses: Clinical Effectiveness and Guidelines. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2016. **KQ1E2a, KQ2E2a, KQ3E2a.**

26. Canadian Agency for Drugs and Technologies in Health. Pharmacological agents for smoking cessation: clinical effectiveness and cost-effectiveness (CADTH rapid response report: reference list). Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

27. Canadian Agency for Drugs and Technologies in Health. Cytisine for Smoking Cessation: Clinical Effectiveness and Cost-Effectiveness. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

28. Carr AB, Ebbert J. Interventions for tobacco cessation in the dental setting. *Cochrane Database Syst Rev*. 2012;6:CD005084. PMID: 22696348. **KQ1E6, KQ2E11, KQ3E6.**

29. Cawkwell PB, Blaum C, Sherman SE. Pharmacological smoking cessation therapies in older adults: a review of the evidence. *Drugs Aging*. 2015;32(6):443-51. PMID: 26025119. https://doi.org/10.1007/s40266-015-0274-9 **KQ1E6, KQ2E12, KQ3E6.**

30. 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. **KQ1E10, KQ2E10, KQ3E10.**

31. Chebli JL, Blaszczynski A, Gainsbury SM. Internet-based interventions for addictive behaviours: a systematic review. *J Gambl Stud*. 2016;32(4):1279-304. PMID: 27002522. https://doi.org/10.1007/s10899-016-9599-5 **KQ1E6, KQ2E12, KQ3E6.**

32. Chen D, Wu LT. Smoking cessation interventions for adults aged 50 or older: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2015;154:14-24. PMID: 26094185. https://doi.org/10.1016/j.drugalcdep.2015.06.004 **KQ1E6, KQ2E12, KQ3E6.**

33. 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. **KQ1E6, KQ2E11, KQ3E6.**

34. Cheng HM, Chung YC, Chen HH, et al. Systematic review and meta-analysis of the effects of acupoint stimulation on smoking cessation. *Am J Chin Med*.

2012;40(3):429-42. PMID: 22745061. **KQ1E6, KQ2E11, KQ3E6.**

35. Civljak M, Stead LF, Hartmann-Boyce J, et al. Internet-based interventions for smoking cessation. *Cochrane Database Syst Rev.* 2013;7:CD007078. PMID: 23839868. **KQ1E6, KQ2E10, KQ3E6.**

36. Claire R, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2020;3:CD010078. PMID: 32129504. https://doi.org/10.1002/14651858.CD010078.pub3 **KQ1E2d, KQ2E2d, KQ3E2d.**

37. Coleman T, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2012;9:CD010078. PMID: 22972148. **KQ1E2d, KQ2E2d, KQ3E2d.**

38. Coleman T, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2015;12:CD010078. PMID: 26690977. https://dx.doi.org/10.1002/14651858.CD010078.pub2 **KQ1E2d, KQ2E2d, KQ3E2d.**

39. de Souza IC, de Barros VV, Gomide HP, et al. Mindfulness-based interventions for the treatment of smoking: a systematic literature review. *J Altern Complement Med.* 2015;21(3):129-40. PMID: 25710798. https://doi.org/10.1089/acm.2013.0471 **KQ1E6, KQ2E7, KQ3E6.**

40. 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;142:14-23. PMID: 25064021. **KQ1E6, KQ2E11, KQ3E11.**

41. Drabkin A. Treatment for tobacco use. https://www.dynamed.com/management/treatment-for-tobacco-use-19/. Accessed Dec 20, 2017. **KQ1E2a, KQ2E2a, KQ3E2a**

42. Drovandi AD, Chen CC, Glass BD. Adverse effects cause varenicline discontinuation: a meta-analysis. *Curr Drug Saf.* 2016;11(1):78-85. PMID: 26412667. **KQ1E6, KQ2E6, KQ3E12.**

43. DynaMed. Counseling for tobacco cessation. https://www.dynamed.com/management/counseling-for-tobacco-cessation. Accessed Dec 20, 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

44. DynaMed. Varenicline. https://www.dynamed.com/drug-monograph/varenicline. Accessed Dec 20, 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

45. Ebbert J, Montori VM, Erwin PJ, et al. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev*. 2011;2:CD004306. PMID: 21328266. **KQ1E6, KQ2E11, KQ3E6.**

46. Evins AE, Cather C, Laffer A. Treatment of tobacco use disorders in smokers with serious mental illness: toward clinical best practices. *Harv Rev Psychiatry*. 2015;23(2):90-8. PMID: 25747922. https://doi.org/10.1097/hrp.0000000000000063 **KQ1E2a, KQ2E2a, KQ3E2a.**

47. Fanshawe TR, Hartmann-Boyce J, Perera R, et al. Competitions for smoking cessation. *Cochrane Database Syst Rev*. 2019;2:CD013272. PMID: 30784046. https://doi.org/10.1002/14651858.Cd013272 **KQ1E4, KQ2E4, KQ3E4.**

48. 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*. 2011;118(12):1422-8. PMID: 21880109. **KQ1E6, KQ2E11, KQ3E6.**

49. Garcia-Gomez L, Hernandez-Perez A, Noe-Diaz V, et al. Smoking cessation treatments: current psychological and pharmacological options. *Rev Invest Clin*. 2019;71(1):7-16. PMID: 30810545.

https://doi.org/10.24875/ric.18002629 **KQ1E2a, KQ2E2a, KQ3E2a.**

50. Gardner K, Kearns R, Woodland L, et al. A scoping review of the evidence on health promotion interventions for reducing waterpipe smoking: implications for practice. *Front Public Health*. 2018;6:308. PMID: 30456210. https://doi.org/10.3389/fpubh.2018.00308 **KQ1E4, KQ2E4, KQ3E4.**

51. Ghorai K, Akter S, Khatun F, et al. mHealth for smoking cessation programs: a systematic review. *J Pers Med*. 2014;4:412-23. PMID: 25563359. https://doi.org/10.3390/jpm4030412 **KQ1E6, KQ2E6, KQ3E6.**

52. 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. Washington, DC: Department of Veterans Affairs; 2010. PMID: 21290640. **KQ1E6, KQ2E11, KQ3E11.**

53. Gomez-Coronado N, Walker AJ, Berk M, et al. Current and emerging pharmacotherapies for cessation of tobacco smoking. *Pharmacotherapy*. 2018;38(2):235-58. PMID: 29250815. 10.1002/phar.2073 **KQ1E2a, KQ2E2a, KQ3E2a.**

54. Gould GS, Lim LL, Mattes J. Prevention and treatment of smoking and tobacco use during pregnancy in selected Indigenous communities in high-income countries of the United States, Canada, Australia, and New Zealand: an evidence-based review. *Chest*. 2017;152(4):853-66. PMID: 28694200. https://dx.doi.org/10.1016/j.chest.2017.06.033 **KQ1E2a, KQ2E2a, KQ3E2a.**

55. Gulliver A, Farrer L, Chan JK, et al. Technology-based interventions for tobacco and other drug use in university and college students: a systematic review and meta-analysis. *Addict Sci Clin Pract*. 2015;10:5. PMID: 25928221. https://doi.org/10.1186/s13722-015-0027-4 **KQ1E6, KQ2E7, KQ3E6.**

56. Hartmann-Boyce J, Lancaster T, Stead LF. Print-based self-help interventions for smoking cessation. *Cochrane Database Syst Rev.* 2014;6:CD001118. PMID: 24888233. **KQ1E6, KQ2E10, KQ3E6.**

57. Haskins BL, Lesperance D, Gibbons P, et al. A systematic review of smartphone applications for smoking cessation. *Transl Behav Med*. 2017;7(2):292-9. PMID: 28527027. https://doi.org/10.1007/s13142-017-0492-2 **KQ1E6, KQ2E6, KQ3E6.**

58. Hendrick V, Suri R, Gitlin MJ, et al. Bupropion use during pregnancy: a systematic review. *Prim Care Companion CNS Disord*. 2017;19(5):21. PMID: 28973846. https://dx.doi.org/10.4088/PCC.17r02160 **KQ1E2d, KQ2E2d, KQ3E2d.**

59. Hettema JE, Hendricks PS. Motivational interviewing for smoking cessation: a meta-analytic review. *J Consult Clin Psychol*. 2010;78(6):868-84. PMID: 21114344. **KQ1E6, KQ2E11, KQ3E6.**

60. Hickson C, Lewis S, Campbell KA, et al. Comparison of nicotine exposure during pregnancy when smoking and abstinent with nicotine replacement therapy: systematic review and meta-analysis. *Addiction*. 2019;114(3):406-24. PMID: 30315598. https://doi.org/10.1111/add.14473 **KQ1E2d, KQ2E2d, KQ3E2d.**

61. Hollands GJ, McDermott MS, Lindson-Hawley N, et al. Interventions to increase adherence to medications for tobacco dependence. *Cochrane Database Syst Rev*. 2015(2):CD009164. PMID: 25914910. https://doi.org/10.1002/14651858.CD009164.pub2 **KQ1E6, KQ2E10, KQ3E10.**

62. Hsieh MT, Tseng PT, Wu YC, et al. Effects of different pharmacologic smoking cessation treatments on body weight changes and success rates in patients with nicotine dependence: a

network meta-analysis. *Obes Rev*. 2019;20(6):895-905. PMID: 30816006. https://doi.org/10.1111/obr.12835 **KQ1E6, KQ2E6, KQ3E6.**

63. 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. *J Public Health*. 2012;20(4):355-65. **KQ1E6, KQ2E11, KQ3E11.**

64. Hubbard G, Gorely T, Ozakinci G, et al. A systematic review and narrative summary of family-based smoking cessation interventions to help adults quit smoking. *BMC Fam Pract*. 2016;17:73. PMID: 27342987. https://doi.org/10.1186/s12875-016-0457-4 **KQ1E6, KQ2E4, KQ3E6.**

65. Hughes JR. Varenicline as a cause of suicidal outcomes. *Nicotine Tob Res*. 2016;18(1):2-9. PMID: 25572451. https://doi.org/10.1093/ntr/ntu275 **KQ1E2a, KQ2E2a, KQ3E2a.**

66. Hughes JR, Stead LF, Hartmann BJ, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014;1:CD000031. PMID: 24402784. **KQ1E6, KQ2E10, KQ3E10.**

67. Hurst D. Nicotine lozenges and behavioural interventions may help smokeless tobacco users to quit. *Evid Based Dent.* 2015;16(4):104-5. PMID: 26680516. https://doi.org/10.1038/sj.ebd.6401129 **KQ1E2a, KQ2E2a, KQ3E2a.**

68. 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;13(4):227-38. PMID: 21350042. **KQ1E6, KQ2E11, KQ3E6.**

69. Jahagirdar D, Kaunelis D. Smoking Cessation Interventions for Patients With Severe Mental Illnesses: A Review of Clinical Effectiveness and Guidelines. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health; 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

70. Jawad M, Jawad S, Waziry RK, et al. Interventions for waterpipe tobacco smoking prevention and cessation: a systematic review. *Sci Rep*. 2016;6:25872. PMID: 27167891. https://doi.org/10.1038/srep25872 **KQ1E6, KQ2E7, KQ3E6.**

71. Kittle J, Lopes RD, Huang M, et al. Cardiovascular adverse events in the drug-development program of bupropion for smoking cessation: a systematic retrospective adjudication effort. *Clin Cardiol.* 2017;40(10):899-906. PMID: 28605035. https://doi.org/10.1002/clc.22744 **KQ1E6, KQ2E6, KQ3E2a.**

72. Lai Douglas TC, Cahill K, Qin Y, et al. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*. 2010;1:CD006936. PMID: 20091612. **KQ1E6, KQ2E11, KQ3E6.**

73. Lee EB, An W, Levin ME, et al. An initial meta-analysis of acceptance and commitment therapy for treating substance use disorders. *Drug Alcohol Depend*. 2015;155:1-7. PMID: 26298552. https://doi.org/10.1016/j.drugalcdep.2015.08.004 **KQ1E6, KQ2E12, KQ3E6.**

74. Lee J, Matthews A, McCullen C, et al. Promotion of tobacco use cessation for lesbian, gay, bisexual, and transgender people: a systematic review. *Am J Prev Med*. 2014;47(6):823-31. PMID: 25455123. https://doi.org/10.1016/j.amepre.2014.07.051 **KQ1E6, KQ2E7, KQ3E6.**

75. Lee PN, Fariss MW. A systematic review of possible serious adverse health effects of nicotine replacement therapy. *Arch Toxicol.* 2017;91(4):1565-94. PMID: 27699443. https://doi.org/10.1007/s00204-016-1856-y **KQ1E6, KQ2E6, KQ3E2d.**

76. Lemhoefer C, Rabe GL, Wellmann J, et al. Emergency department-initiated tobacco control: update of a systematic review and meta-analysis of randomized controlled trials. *Prev Chronic Dis*. 2017;14:E89. PMID: 28981403. https://doi.org/10.5888/pcd14.160434 **KQ1E6, KQ2E7, KQ3E6.**

77. Leung LW, Davies GA. Smoking cessation strategies in pregnancy. *J Obstet Gynaecol Can*. 2015;37(9):791-7. PMID: 26605448. https://dx.doi.org/10.1016/S1701-2163(15)30149-3 **KQ1E2a, KQ2E2a, KQ3E2a.**

78. Likis F, Andrews J, Fonnesbeck C, et al. Smoking Cessation Interventions in Pregnancy and Postpartum Care. Rockville, MD: 2014. **KQ1E11, KQ2E11, KQ3E11.**

79. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*. 2015;3:CD006936. https://doi.org/10.1002/14651858.CD006936.pub3 **KQ1E6, KQ2E10, KQ3E6.**

80. Lumley J, Chamberlain C, Dowswell T, et al. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2009;3:CD001055. PMID: 19588322. **KQ1E11, KQ2E11, KQ3E11.**

81. Maglione MA, Maher AR, Ewing B, et al. Efficacy of mindfulness meditation for smoking cessation: a systematic review and meta-analysis. *Addict Behav*. 2017;69:27-34. PMID: 28126511. https://doi.org/10.1016/j.addbeh.2017.01.022 **KQ1E6, KQ2E7, KQ3E6.**

82. Martin Cantera C, Puigdomenech E, Ballve JL, et al. Effectiveness of multicomponent interventions in primary healthcare settings to promote continuous smoking cessation in adults: a systematic review. *BMJ Open*. 2015;5(10):e008807. PMID: 26428333. https://doi.org/10.1136/bmjopen-2015-008807 **KQ1E6, KQ2E12, KQ3E6.**

83. Maziak W, Jawad M, Jawad S, et al. Interventions for waterpipe smoking cessation. *Cochrane Database Syst Rev*. 2015;7:CD005549. PMID: 26228266. https://doi.org/10.1002/14651858.CD005549.pub3 **KQ1E8, KQ2E8, KQ3E8.**

84. Merriel S, Andrews V, Salisbury C. Telehealth interventions for primary prevention of cardiovascular disease: a systematic review and meta-analysis. *Prev Med.* 2014;64:88-95. PMID: 24726502. https://doi.org/10.1016/j.ypmed.2014.04.001 **KQ1E1, KQ2E1, KQ3E1.**

85. 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. *Ann Med.* 2012;44(6):588-97. PMID: 22860882. **KQ1E6, KQ2E11, KQ3E6.**

86. Momin B, Neri A, McCausland K, et al. Traditional and innovative promotional strategies of tobacco cessation services: a review of the literature. *J Community Health*. 2014;39(4):800-9. PMID: 24515948. https://doi.org/10.1007/s10900-014-9825-y **KQ1E1, KQ2E1, KQ3E1.**

87. Montgomery L, Robinson C, Seaman EL, et al. A scoping review and meta-analysis of psychosocial and pharmacological treatments for cannabis and tobacco use among African Americans. *Psychol Addict Behav.* 2017;31(8):922-43. PMID: 29199844. https://doi.org/10.1037/adb0000326 **KQ1E6, KQ2E12, KQ3E6.**

88. Morales-Rosado JA, Cousin MA, Ebbert JO, et al. A critical review of repurposing apomorphine for smoking cessation. *Assay Drug Dev Technol*. 2015;13(10):612-22. PMID: 26690764. https://doi.org/10.1089/adt.2015.680 **KQ1E2a, KQ2E2a, KQ3E2a.**

89. Morozova M, Rabin RA, George TP. Co-morbid tobacco use disorder and depression: a re-evaluation of smoking cessation therapy in depressed smokers. *Am J Addict*. 2015;24(8):687-94. PMID: 26354720. https://doi.org/10.1111/ajad.12277 **KQ1E12, KQ2E12, KQ3E12.**

90. Mottillo S, Filion KB, Belisle P, et al. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2009;30(6):718-30. PMID: 19109354. **KQ1E6, KQ2E11, KQ3E6.**

91. Muhlig S, Paulick J, Lindenmeyer J, et al. Applying the 'cognitive bias modification' concept to smoking cessation-a systematic review. *Sucht*. 2016;62(6):333-54. http://dx.doi.org/10.1024/0939-5911/a000454 **KQ1E6, KQ2E6, KQ3E6.**

92. Myung SK, Ju W, Jung HS, et al. Efficacy and safety of pharmacotherapy for smoking cessation among pregnant smokers: a meta-analysis. *BJOG*. 2012;119(9):1029-39. PMID: 22780818. **KQ1E2d, KQ2E2d, KQ3E2d.**

93. Myung SK, McDonnell DD, Kazinets G, et al. Effects of Web- and computer-based smoking cessation programs. *Arch Intern Med*. 2009;169(10):929-37. PMID: 19468084. **KQ1E6, KQ2E11, KQ3E6.**

94. Naslund JA, Kim SJ, Aschbrenner KA, et al. Systematic review of social media interventions for smoking cessation. *Addict Behav*. 2017;73:81-93. PMID: 28499259. https://doi.org/10.1016/j.addbeh.2017.05.002 **KQ1E6, KQ2E7, KQ3E6.**

95. Nethan ST, Sinha DN, Chandan K, et al. Smokeless tobacco cessation interventions: a systematic review. *Indian J Med Res*. 2018;148(4):396-410. PMID: 30666002. https://doi.org/10.4103/ijmr.IJMR_1983_17 **KQ1E6, KQ2E12, KQ3E6.**

96. 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. **KQ1E6, KQ2E11, KQ3E6.**

97. Norris AR, Miller JE. Motivational interviewing or counseling, medical therapies or no intervention to improve tobacco cessation in adults and adolescents. *J Okla State Med Assoc*. 2017;110(3):142-3. PMID: 29298020. **KQ1E2a, KQ2E2a, KQ3E2a.**

98. Oikonomou MT, Arvanitis M, Sokolove RL. Mindfulness training for smoking cessation: a meta-analysis of randomized-controlled trials. *J Health Psychol*. 2017;22(14):1841-50. PMID: 27044630. https://doi.org/10.1177/1359105316637667 **KQ1E6, KQ2E7, KQ3E6.**

99. Omana-Cepeda C, Jane-Salas E, Estrugo-Devesa A, et al. Effectiveness of dentist's intervention in smoking cessation: a review. *J Clin Exp Dent*. 2016;8(1):e78-83. PMID: 26855711. https://doi.org/10.4317/jced.52693 **KQ1E6, KQ2E12, KQ3E6.**

100. Oosterveen E, Tzelepis F, Ashton L, et al. A systematic review of eHealth behavioral interventions targeting smoking, nutrition, alcohol, physical activity and/or obesity for young adults. *Prev Med*. 2017;99:197-206. PMID: 28130046. https://doi.org/10.1016/j.ypmed.2017.01.009 **KQ1E6, KQ2E7, KQ3E6.**

101. Park E. Behavioral approaches to smoking cessation. https://www.uptodate.com/contents/behavioral-approaches-to-smoking-cessation. Accessed Dec 13, 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

102. Peletidi A, Nabhani-Gebara S, Kayyali R. Smoking cessation support services at community pharmacies in the UK: a systematic review. *Hellenic J Cardiol*.

2016;57(1):7-15. PMID: 26856195. **KQ1E4, KQ2E4, KQ3E4.**

103. Posadzki P, Choi J, Lee M, et al. Yoga for addictions: a systematic review of randomised clinical trials (Provisional abstract). *Focus Altern Complement Ther*. 2014;19(1):1-8. **KQ1E6, KQ2E6, KQ3E6.**

104. 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. **KQ1E6, KQ2E6, KQ3E10.**

105. Ramseier CA, Suvan JE. Behaviour change counselling for tobacco use cessation and promotion of healthy lifestyles: a systematic review. *J Clin Periodontol.* 2015;42(Suppl 16):S47-58. PMID: 25496370. https://doi.org/10.1111/jcpe.12351 **KQ1E6, KQ2E2a, KQ3E6.**

106. Rice VH, Hartmann-Boyce J, Stead LF. Nursing interventions for smoking cessation. *Cochrane Database Syst Rev*. 2013;8:CD001188. PMID: 23939719. **KQ1E6, KQ2E10, KQ3E6.**

107. Rigotti N. Benefits and risks of smoking cessation. https://www.uptodate.com/contents/benefits-and-risks-of-smoking-cessation. Accessed Dec 13, 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

108. Rigotti NA. Overview of smoking cessation management in adults. https://www.uptodate.com/contents/overview-of-smoking-cessation-management-in-adults. Accessed Dec 13, 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

109. Rigotti NA. Pharmacotherapy for smoking cessations in adults. https://www.uptodate.com/contents/pharmacotherapy-for-smoking-cessation-in-adults. Accessed Dec 13, 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

110. Schwindt R, Hudmon KS, Knisely M, et al. Impact of tobacco quitlines on smoking cessation in persons with mental illness: a systematic review. *J Drug Educ*. 2017;47(1-2):68-81. PMID: 29534595. https://doi.org/10.1177/0047237918762104 **KQ1E12, KQ2E12, KQ3E6.**

111. Scott-Sheldon LA, Lantini R, Jennings EG, et al. Text messaging-based interventions for smoking cessation: a systematic review and meta-analysis. *JMIR mHealth uHealth*. 2016;4(2):e49. PMID: 27207211. https://doi.org/10.2196/mhealth.5436 **KQ1E6, KQ2E7, KQ3E6.**

112. Secades-Villa R, Gonzalez-Roz A, Garcia-Perez A, et al. Psychological, pharmacological, and combined smoking cessation interventions for smokers with current depression: a systematic review and meta-analysis. *PLoS One*. 2017;12(12):e0188849. PMID: 29206852. https://doi.org/10.1371/journal.pone.0188849 **KQ1E6, KQ2E12, KQ3E12.**

113. Shahab L, McEwen A. Online support for smoking cessation: a systematic review of the literature. *Addiction*. 2009;104(11):1792-804. PMID: 19832783. **KQ1E6, KQ2E11, KQ3E6.**

114. Si S, Moss J, Sullivan T, et al. Effectiveness of general practice-based health checks: a systematic review and meta-analysis (Structured abstract). *Br J Gen Pract.* 2014;64(618):e47-e53. **KQ1E1, KQ2E1, KQ3E1.**

115. Spohr SA, Nandy R, Gandhiraj D, et al. Efficacy of SMS text message interventions for smoking cessation: a meta-analysis. *J Subst Abuse Treat*. 2015;56:1-10. PMID: 25720333. https://doi.org/10.1016/j.jsat.2015.01.011 **KQ1E6, KQ2E12, KQ3E6.**

116. Stead LF, Hartmann BJ, Perera R, et al. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev*. 2013;8:CD002850. PMID: 23934971. **KQ1E6, KQ2E10, KQ3E6.**

117. Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev*. 2015;10:CD009670. PMID: 26457723. https://dx.doi.org/10.1002/14651858.CD009670.pub3 **KQ1E6, KQ2E10, KQ3E6.**

118. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2012;10:CD008286. PMID: 23076944. **KQ1E6, KQ2E10, KQ3E6.**

119. Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane *Database Syst Rev*. 2013;12:CD009670. PMID: 23235680. **KQ1E6, KQ2E10, KQ3E6.**

120. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;11:CD000146. PMID: 23152200. **KQ1E6, KQ2E10, KQ3E10.**

121. Stubbs B, Vancampfort D, Bobes J, et al. How can we promote smoking cessation in people with schizophrenia in practice? A clinical overview. *Acta Psychiatr Scand.* 2015;132(2):122-30. PMID: 25754402. https://doi.org/10.1111/acps.12412 **KQ1E2a, KQ2E2a, KQ3E2a.**

122. Su A, Buttenheim AM. Maintenance of smoking cessation in the postpartum period: which interventions work best in the long-term? *Matern Child Health J*. 2014;18(3):714-28. PMID: 23812798. **KQ1E6, KQ2E11, KQ3E6.**

123. Sun Y, Duan W, Meng X, et al. Varenicline is associated with a modest limitation in weight gain in smokers after smoking cessation: a meta-analysis. *J Public Health (Oxf).* 2018;40(2):e126-e132. PMID: 28505296. https://doi.org/10.1093/pubmed/fdx056 **KQ1E6, KQ2E6, KQ3E12.**

124. Tahiri M, Mottillo S, Joseph L, et al. Alternative smoking cessation aids: a meta-analysis of randomized controlled trials. *Am J Med*. 2012;125(6):576-84. PMID: 22502956. **KQ1E6, KQ2E11, KQ3E6.**

125. Thomas KH, Caldwell D, Dalili MN, et al. How do smoking cessation medicines compare with respect to their neuropsychiatric safety? A protocol for a systematic review, network meta-analysis and cost-effectiveness analysis. *BMJ Open*. 2017;7(6):e015414. PMID: 28624760. https://doi.org/10.1136/bmjopen-2016-015414 **KQ1E2a, KQ2E2a, KQ3E2a.**

126. Tran K, Argáez C. Smoking Reduction and Cessation Interventions for Pregnant Women and Mothers of Infants: A Review of the Clinical Effectiveness. Ottawa: CADTH; 2017. **KQ1E2a, KQ2E2a, KQ3E2a.**

127. Tran K, Asakawa K, Cimon K, et al. Pharmacologic-based strategies for smoking cessation: clinical and cost-effectiveness analyses. *CADTH Technol Overv.* 2012;2(3):e2303. **KQ1E6, KQ2E11, KQ3E11.**

128. Turner E, Jones M, Vaz LR, et al. Systematic review and meta-analysis to assess the safety of buproprion and varenicline in pregnancy. *Nicotine Tob Res.* 2019;21(8):1001-1010. PMID: 29579233. https://doi.org/10.1093/ntr/nty055 **KQ1E2d, KQ2E2d, KQ3E2d.**

129. Tutka P, Vinnikov D, Courtney RJ, et al. Cytisine for nicotine addiction treatment: a review of pharmacology, therapeutics and an update of clinical trial evidence for smoking cessation. *Addiction*. 2019;[Epub ahead of print]. PMID: 31240783. https://doi.org/10.1111/add.14721 **KQ1E6, KQ2E12, KQ3E12.**

130. 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;103(12):922-41. PMID: 21666098. **KQ1E6, KQ2E11, KQ3E6.**

131. Tzelepis F, Paul CL, Williams CM, et al. Real-time video counselling for smoking cessation. *Cochrane Database Syst Rev*. 2019;10:CD012659. https://doi.org/10.1002/14651858.CD012659 **KQ1E2a, KQ2E2a, KQ3E2a.**

132. Ussher MH, Taylor AH, Faulkner GE. Exercise interventions for smoking cessation. *Cochrane Database Syst Rev*. 2014;8:CD002295. PMID: 25170798. **KQ1E6, KQ2E10, KQ3E6.**

133. Veisani Y, Jenabi E, Delpisheh A, et al. Effect of prenatal smoking cessation interventions on birth weight: meta-analysis. *J Matern Fetal Neonatal Med*. 2019;32(2):332-8. PMID: 28889768. https://doi.org/10.1080/14767058.2017.1378335 **KQ1E12, KQ2E12, KQ3E6.**

134. Villanti AC, McKay HS, Abrams DB, et al. Smoking-cessation interventions for U.S. young adults: a systematic review. *Am J Prev Med.* 2010;39(6):564-74. PMID: 21084078. **KQ1E6, KQ2E12, KQ3E6.**

135. Vogeler T, McClain C, Evoy KE. Combination bupropion SR and varenicline for smoking cessation: a systematic review. *Am J Drug Alcohol Abuse.* 2016;42(2):129-39. PMID: 26809272. 10.3109/00952990.2015.1117480 **KQ1E6, KQ2E12, KQ3E12.**

136. Ward KD, Siddiqi K, Ahluwalia JS, et al. Waterpipe tobacco smoking: the critical need for cessation treatment. *Drug Alcohol Depend*. 2015;153:14-21. PMID: 26054945. https://doi.org/10.1016/j.drugalcdep.2015.05.029 **KQ1E2a, KQ2E2a, KQ3E2a.**

137. Washio Y, Cassey H. Systematic review of interventions for racial/ethnic-minority pregnant smokers. *J Smok Cessat*. 2016;11(1):12-27. PMID: 26925170. https://doi.org/10.1017/jsc.2014.12 **KQ1E12, KQ2E12, KQ3E6.**

138. Whittaker R, McRobbie H, Bullen C, et al. Mobile phone-based interventions for smoking cessation. *Cochrane Database Syst Rev.* 2012;11:CD006611. PMID: 23152238. **KQ1E6, KQ2E10, KQ3E6.**

139. Whittaker R, McRobbie H, Bullen C, et al. Mobile phone-based interventions for smoking cessation. *Cochrane Database Syst Rev.* 2016;4:CD006611. PMID: 27060875. https://doi.org/10.1002/14651858.CD006611.pub4 **KQ1E6, KQ2E10, KQ3E6.**

140. Wray JM, Funderburk JS, Acker JD, et al. A meta-analysis of brief tobacco interventions for use in integrated primary care. *Nicotine Tob Res*. 2018;20(12):1418-1426. PMID: 29059419. https://doi.org/10.1093/ntr/ntx212 **KQ1E6, KQ2E12, KQ3E6.**

141. Ybarra ML, Jiang Y, Free C, et al. Participant-level meta-analysis of mobile phone-based interventions for smoking cessation across different countries. *Prev Med.* 2016;89:90-7. PMID: 27154349. https://doi.org/10.1016/j.ypmed.2016.05.002 **KQ1E2a, KQ2E2a, KQ3E2a.**

142. Zbikowski SM, Magnusson B, Pockey JR, et al. A review of smoking cessation interventions for smokers aged 50 and older. *Maturitas*. 2012;71(2):131-41. PMID: 22209349. **KQ1E6, KQ2E12, KQ3E6.**

Appendix E List 2. Excluded Studies List, Tobacco Cessation in Adults: Electronic Cigarettes

Exclusion Code	Definition
E1	Study aim not relevant
E2	Study design
E3	Population
E4	**Outcomes**: No relevant outcomes (exclude trials that only report tobacco reduction; reduction in withdrawal symptoms; attitudes, knowledge, beliefs; intentions; etc.)
E5	Setting
E6	Poor Quality
E7	Publication Type

1. [No author listed]. Correction to: Electronic cigarette use and myocardial infarction among adults in the US population: assessment of tobacco and health (*J Am Heart Assoc*, (2019), 8, 12, 10.1161/JAHA.119.012317). J Am Heart Assoc. 8(21). 2019. **KQ1E2, KQ2E2, KQ3E2**
2. [No author listed]. Retraction to: Electronic cigarette use and myocardial infarction among adults in the US population: assessment of tobacco and health. *J Am Heart Assoc*. 2020;9(4):e014519. **KQ1E2, KQ2E2, KQ3E2**
3. Brownson EG, Thompson CM, et al. Explosion injuries from e-cigarettes. *N Engl J Med*. 2016;375(14):1400-1402. PMID: 27705271. https://dx.doi.org/doi:10.1056/NEJMc1608478 **KQ1E2, KQ2E2, KQ3E2**
4. Baldassarri SR, Bernstein SL, et al. Electronic cigarettes for adults with tobacco dependence undergoing a tobacco treatment program: a pilot prospective study. *Am J Respir Crit Care Med.* 2016;193(Meeting Abstracts):A6511. **KQ1E4, KQ2E6, KQ3E4**
5. Baldassarri SR, Bernstein SL, et al. Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: a pilot study. *Addict Behav*. 2018;80:1-5. PMID: 29304395. https://dx.doi.org/10.1016/j.addbeh.2017.11.033 **KQ1E4, KQ2E6, KQ3E4**
6. Barkat SS, Tellier SM, et al. Varenicline for cessation from nicotine-containing electronic cigarettes. *Am J Health Syst Pharm*. 2019;76(23):1894-1895. **KQ1E2, KQ2E2, KQ3E2**
7. Beard E, Brown J, et al. Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis. *BMJ Open*. 2018;8(6):e016046. PMID: 29921676. https://dx.doi.org/10.1136/bmjopen-2017-016046 **KQ1E4, KQ2E2, KQ3E4**
8. Benmarhnia T, Pierce JP, et al. Can e-cigarettes and pharmaceutical aids increase smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers. *Am J Epidemiol*. 2018;187(11):2397-2404. PMID: 29955810. https://dx.doi.org/10.1093/aje/kwy129 **KQ1E4, KQ2E2, KQ3E4**
9. Bhatta DN, Glantz SA. Association of e-cigarette use with respiratory disease among adults: a longitudinal analysis. *Am J Prev Med*. 2020;58(2):182-90. **KQ1E2, KQ2E4, KQ3E4**
10. Bhatta DN, Glantz SA. Electronic cigarette use and myocardial infarction among adults in the US population assessment of tobacco and health. *J Am Heart Assoc.* 2019;8(12):e012317. **KQ1E2, KQ2E2, KQ3E2**
11. Blagev DP, Harris D, et al. Clinical presentation, treatment, and short-term

outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. *Lancet*. 2019;394(10214):2073-2083. **KQ1E2, KQ2E2, KQ3E2**

12. Borrelli B, O'Connor GT. E-cigarettes to assist with smoking cessation. *N Engl J Med*. 2019;380(7):678-679. PMID: 30699299. https://dx.doi.org/10.1056/NEJMe1816406 **KQ1E2, KQ2E2, KQ3E2**
13. Brady BR, Crane TE, et al. Electronic cigarette use and tobacco cessation in a state-based quitline. *J Smok Cessat*. 2019;14(3):176-185. https://dx.doi.org/10.1017/jsc.2019.2 **KQ1E4, KQ2E2, KQ3E4**
14. Campagna D, Cibella F, et al. Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. *Eur J Clin Invest*. 2016;46(8):698-706. PMID: 27322745. https://dx.doi.org/10.1111/eci.12651 **KQ1E4, KQ2E4, KQ3E4**
15. Cibella F, Campagna D, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)*. 2016;130(21):1929-37. PMID: 27543458. https://dx.doi.org/10.1042/cs20160268 **KQ1E4, KQ2E4, KQ3E4**
16. Coleman BN, Rostron B, et al. Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2014. *Tob Control*. 2017;26(e2):e117-e126. PMID: 28624763. https://dx.doi.org/10.1136/tobaccocontrol-2016-053462 **KQ1E2, KQ2E2, KQ3E4**
17. Collins SE, Nelson LA, et al. Harm reduction treatment for smoking (HaRT-S): findings from a single-arm pilot study with smokers experiencing chronic homelessness. *Subst Abus*. 2019;40(2):229-239. PMID: 30924732. https://dx.doi.org/10.1080/08897077.2019.1572049 **KQ1E2, KQ2E2, KQ3E4**
18. Dahal R, Adhikari K, et al. Smoking cessation and improvement in mental health outcomes: do people who quit smoking by switching to electronic cigarettes experience improvement in mental health? *Can J Psychiatry*. 2020;65(7):512-514. **KQ1E2, KQ2E2, KQ3E2**
19. Dobbie F, Hiscock R, et al. Evaluating Long-term Outcomes of NHS Stop Smoking Services (ELONS): a prospective cohort study. *Health Technol Assess*. 2015;19(95):1-156. PMID: 26565129. https://dx.doi.org/10.3310/hta19950 **KQ1E1, KQ2E1, KQ3E1**
20. Eisenhofer J, Makanjuola T, et al. Efficacy of electronic cigarettes for smoking cessation in veterans. Drug Alcohol Depend. 2015;156:e63-e64. https://dx.doi.org/10.1016/j.drugalcdep.2015.07.1091 **KQ1E7, KQ2E7, KQ3E7**
21. Ely J. Evaluation of the Use of Electric Cigarettes in a Rural Smoking Cessation Program. College of Natural and Health Sciences. Doctor of Nursing Practice. 2013. **KQ1E2, KQ2E2, KQ3E2**
22. Fairchild AL, Lee JS, et al. E-cigarettes and the harm-reduction continuum. *N Engl J Med.* 2018;378(3):216-219. PMID: 29342380. https://dx.doi.org/10.1056/NEJMp1711991 **KQ1E1, KQ2E1, KQ3E1**
23. Farsalinos K, Niaura R. E-cigarettes and smoking cessation in the United States according to frequency of e-cigarette use and quitting duration: analysis of the 2016 and 2017 National Health Interview Surveys. *Nicotine Tob Res*. 2020;22(5):655-662. PMID: 30768136. https://dx.doi.org/10.1093/ntr/ntz025 **KQ1E4, KQ2E2, KQ3E4**
24. Felicione NJ, Enlow P, et al. A pilot investigation of the effect of electronic

cigarettes on smoking behavior among opioid-dependent smokers. *Addict Behav.* 2019;91:45-50. PMID: 30006020. https://dx.doi.org/10.1016/j.addbeh.2018.07.003 **KQ1E2, KQ2E2, KQ3E4**

25. Ferrari M, Zanasi A, et al. Short-term physiological effects of the e-cigarette compared to regular cigarette. *Eur Respir J*. 2014;44:3436. **KQ1E2, KQ2E2, KQ3E2**
26. Franco T, Trapasso S, et al. Electronic cigarette: role in the primary prevention of oral cavity cancer. *Clin Med Insights Ear Nose Throat.* 2016;9:7-12. PMID: 27773997. https://dx.doi.org/10.4137/cment.s40364 **KQ1E2, KQ2E2, KQ3E2**
27. Goniewicz ML, Gawron M, et al. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study. *Nicotine Tob Res*. 2017;19(2):160-167. PMID: 27613896. https://dx.doi.org/10.1093/ntr/ntw160 **KQ1E2, KQ2E2, KQ3E2**
28. Goniewicz ML, Smith DM, et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. *JAMA Netw Open*. 2018;1(8):e185937. PMID: 30646298. https://dx.doi.org/10.1001/jamanetworkopen.2018.5937 **KQ1E1, KQ2E1, KQ3E4**
29. Halpern SD, Harhay MO, et al. A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. *N Engl J Med*. 2018;378(24):2302-2310. PMID: 29791259. https://dx.doi.org/10.1056/NEJMsa1715757 **KQ1E4, KQ2E1, KQ3E4**
30. Ikonomidis I, Vlastos D, et al. Electronic cigarette smoking increases arterial stiffness and oxidative stress to a lesser extent than a single conventional cigarette: an acute and chronic study. *Circulation*. 2018;137(3):303-306. PMID: 29335291. https://dx.doi.org/10.1161/circulationaha.117.029153 **KQ1E2, KQ2E2, KQ3E4**
31. Johnson L, Ma Y, et al. E-cigarette usage is associated with increased past-12-month quit attempts and successful smoking cessation in two US population-based surveys. *Nicotine Tob Res.* 2019;21(10):1331-1338. PMID: 30304476. https://dx.doi.org/10.1093/ntr/nty211 **KQ1E4, KQ2E2, KQ3E4**
32. King JL, Reboussin BA, et al. Tobacco product use and mental health status among young adults. *Addict Behav*. 2018;77:67-72. https://dx.doi.org/http://dx.doi.org/10.1016/j.addbeh.2017.09.012 **KQ1E1, KQ2E1, KQ3E1**
33. King JL, Reboussin BA, et al. Adverse symptoms users attribute to e-cigarettes: results from a national survey of US adults. *Drug Alcohol Depend*. 2019;196:9-13. PMID: 30658221. https://dx.doi.org/10.1016/j.drugalcdep.2018.11.030 **KQ1E4, KQ2E4, KQ3E2**
34. Lee SM, Tenney R, et al. The end perioperative smoking pilot study: a randomized trial comparing e-cigarettes versus nicotine patch. *Can J Anesthesia*. 2017;64(1 Supplement 1):S48-s49. https://dx.doi.org/10.1007/s12630-017-1003-0 **KQ1E7, KQ2E7, KQ3E7**
35. Manzoli L, Flacco ME, et al. Cohort study of electronic cigarette use: effectiveness and safety at 24 months. *Tob Control*. 2017;26(3):284-292. PMID: 27272748. https://dx.doi.org/10.1136/tobaccocontrol-2015-052822 **KQ1E2, KQ2E2, KQ3E2**
36. Martinez U, Martinez-Loredo V, et al. How does smoking and nicotine dependence change after onset of vaping? A retrospective analysis of dual users. *Nicotine Tob Res*.

2020;22(5):764-770. PMID: 30883640. https://dx.doi.org/10.1093/ntr/ntz043 **KQ1E4, KQ2E2, KQ3E4**

37. Meier E, Wahlquist AE, et al. A pilot randomized crossover trial of electronic cigarette sampling among smokers. *Nicotine Tob Res*. 2017;19(2):176-182. PMID: 27613880. https://dx.doi.org/10.1093/ntr/ntw157 **KQ1E4, KQ2E4, KQ3E4**
38. Motooka Y, Matsui T, et al. Adverse events of smoking cessation treatments (nicotine replacement therapy and non-nicotine prescription medication) and electronic cigarettes in the Food and Drug Administration Adverse Event Reporting System, 2004-2016. *SAGE Open Med*. 2018;6:2050312118777953. PMID: 29844912. https://dx.doi.org/10.1177/2050312118777953 **KQ1E1, KQ2E1, KQ3E2**
39. Nolan M, Leischow S, et al. Feasibility of electronic nicotine delivery systems in surgical patients. *Nicotine Tob Res*. 2016;18(8):1757-62. PMID: 26834051. https://dx.doi.org/10.1093/ntr/ntw003 **KQ1E4, KQ2E4, KQ3E4**
40. Nowariak EN, Lien RK, et al. E-cigarette use among treatment-seeking smokers: moderation of abstinence by use frequency. *Addict Behav*. 2018;77:137-142. https://dx.doi.org/http://dx.doi.org/10.1016/j.addbeh.2017.09.023 **KQ1E2, KQ2E2, KQ3E4**
41. Osei AD, Mirbolouk M, et al. The association between e-cigarette use and cardiovascular disease among never and current combustible cigarette smokers: BRFSS 2016 & 2017. *Am J Med*. 2019;132(8):949-954.e2. PMID: 30853474. https://dx.doi.org/10.1016/j.amjmed.2019.02.016 **KQ1E2, KQ2E2, KQ3E4**
42. Papaseit E, Perez-Mana C, et al. Pharmacodynamics of nicotine from secondgeneration electronic cigarette. *Basic Clin Pharmacol Toxicol*. 2014;115:13. https://dx.doi.org/10.1111/bcpt.12300 **KQ1E2, KQ2E2, KQ3E2**
43. Park SH, Lee L, et al. Patterns of electronic cigarette use and level of psychological distress. *PLoS One*. 2017;12(3):e0173625. PMID: 28278239. https://dx.doi.org/10.1371/journal.pone.0173625 **KQ1E1, KQ2E1, KQ3E1**
44. Pepper JK, Gilkey MB, et al. Physicians' counseling of adolescents regarding e-cigarette use. *J Adolesc Health*. 2015;57(6):580-586. PMID: 26297135. https://dx.doi.org/10.1016/j.jadohealth.2015.06.017 **KQ1E3, KQ2E3, KQ3E3**
45. Perkins KA, Karelitz JL, et al. Effects of nicotine versus placebo e-cigarette use on symptom relief during initial tobacco abstinence. *Exp Clin Psychopharmacol*. 2017;25(4):249-254. PMID: 28650184. https://dx.doi.org/10.1037/pha0000134 **KQ1E1, KQ2E1, KQ3E1**
46. Pravettoni G, Masiero M, et al. The role of electronic cigarettes in smoking cessation among heavy smokers undergoing a lung cancer screening program: preliminary results of a randomized controlled study. *Psychooncology*. 2016;25:72. https://dx.doi.org/10.1002/pon.4082 **KQ1E2, KQ2E2, KQ3E4**
47. Rossheim ME, Livingston MD, et al. Electronic cigarette explosion and burn injuries, US emergency departments 2015-2017. *Tob Control*. 2019;28(4):472-474. PMID: 30219795. https://dx.doi.org/10.1136/tobaccocontrol-2018-054518 **KQ1E4, KQ2E4, KQ3E2**
48. Russo C, Cibella F, et al. Evaluation of post cessation weight gain in a 1-year randomized smoking cessation trial of electronic cigarettes. *Sci Rep*. 2016;6:18763. PMID: 26729619. https://dx.doi.org/10.1038/srep18763 **KQ1E4, KQ2E4, KQ3E4**

49. Salloum RG, Lee J, et al. Evidence-based tobacco treatment utilization among dual users of cigarettes and E-cigarettes. *Prev Med*. 2018;114:193-199. PMID: 30026117. https://dx.doi.org/10.1016/j.ypmed.2018.07.010 **KQ1E4, KQ2E4, KQ3E4**

50. Shahab L, Goniewicz ML, et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. *Ann Intern Med*. 2017;166(6):390-400. PMID: 28166548. https://dx.doi.org/10.7326/m16-1107 **KQ1E2, KQ2E4, KQ3E4**

51. Sharma R, Gartner CE, et al. The challenge of reducing smoking in people with serious mental illness. *Lancet Respir Med*. 2016;4(10):835-844. PMID: 27707462. https://dx.doi.org/10.1016/s2213-2600(16)30228-4 **KQ1E1, KQ2E1, KQ3E1**

52. Soneji S. Errors in data input in meta-analysis on association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults. *JAMA Pediatr*. 2018;172(1):92-93. PMID: 29131876. https://dx.doi.org/10.1001/jamapediatrics.2017.4200 **KQ1E1, KQ2E1, KQ3E1**

53. Soule EK, Nasim A, et al. Adverse effects of electronic cigarette use: a concept mapping approach. *Nicotine Tob Res*. 2016;18(5):678-85. PMID: 26563262. https://dx.doi.org/10.1093/ntr/ntv246 **KQ1E2, KQ2E2, KQ3E2**

54. Soule EK, Plunk AD, et al. Longitudinal analysis of associations between reasons for electronic cigarette use and change in smoking status among adults in the Population Assessment of Tobacco and Health Study. *Nicotine Tob Res*. 2020;22(5):663-671. PMID: 30698815. https://dx.doi.org/10.1093/ntr/ntz005 **KQ1E4, KQ2E2, KQ3E4**

55. Veldheer S, Yingst J, et al. Pulmonary and other health effects of electronic cigarette use among adult smokers participating in a randomized controlled smoking reduction trial. *Addict Behav*. 2019;91:95-101. PMID: 30393015. https://dx.doi.org/10.1016/j.addbeh.2018.10.041 **KQ1E2, KQ2E2, KQ3E4**

56. Vlachopoulos C, Ioakeimidis N, et al. Electronic cigarette smoking increases aortic stiffness and blood pressure in young smokers. *J Am Coll Cardiol*. 2016;67(23):2802-2803. PMID: 27282901. https://dx.doi.org/10.1016/j.jacc.2016.03.569 **KQ1E2, KQ2E2, KQ3E2**

57. Walele T, Sharma G, et al. A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part B: safety and subjective effects. *Regul Toxicol Pharmacol*. 2016;74:193-9. PMID: 26702788. https://dx.doi.org/10.1016/j.yrtph.2015.12.004 **KQ1E4, KQ2E4, KQ3E2**

58. Wang JB, Olgin JE, et al. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. *PLoS One*. 2018;13(7):e0198681. PMID: 30044773. https://dx.doi.org/10.1371/journal.pone.0198681 **KQ1E2, KQ2E2, KQ3E2**

59. Weaver SR, Huang J, et al. Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015-2016. *PLoS One*. 2018;13(7):e0198047. PMID: 29985948. https://dx.doi.org/10.1371/journal.pone.0198047 **KQ1E4, KQ2E2, KQ3E4**

Appendix E List 3. Excluded Studies List, Tobacco Cessation in Adults: Pharmacotherapy in Pregnant Women

Exclusion Code	Definition
E1	Study aim not relevant
E2	Study design
E3	Population
E4	**Outcomes**: No relevant outcomes (exclude trials that only report tobacco reduction; reduction in withdrawal symptoms; attitudes, knowledge, beliefs; intentions; etc.)
E5	Setting
E6	Poor Quality
E7	Publication Type
E8	Intervention Type

1. Alwan S, Reefhuis J, et al. Maternal use of bupropion and risk for congenital heart defects. *Am J Obstet Gynecol*. 2010;203(1):52e1-6. PMID: 20417496. https://dx.doi.org/10.1016/j.ajog.2010.02.015 **KQ1E2, KQ2E2, KQ3E2**
2. Anonymous. Smoking cessation during pregnancy. *Prescrire Int*. 2015;24(161):157-9. PMID: 26436173. **KQ1E2, KQ2E2, KQ3E2**
3. Bar-Zeev Y, Bovill M, et al. Improving smoking cessation care in pregnancy at Aboriginal Medical Services: 'ICAN QUIT in Pregnancy' step-wedge cluster randomised study. *BMJ Open*. 2019;9(6):e025293. **KQ1E4, KQ2E4, KQ3**
4. Bar-Zeev Y, Bovill M, et al. The indigenous counselling and nicotine (ICAN) quit in pregnancy intervention-preliminary findings of changes in health providers' knowledge and practices. Asia-pacific journal of clinical oncology. Conference: hunter cancer research symposium 2017. Australia. 2017;13(Supplement 5):30-31. https://dx.doi.org/10.1111/ajco.12813 **KQ1E7, KQ2E7, KQ3E7**
5. Boshier A, Wilton LV, et al. Evaluation of the safety of bupropion (Zyban) for smoking cessation from experience gained in general practice use in England in 2000. *Eur J Clin Pharmacol*. 2003;59(10):767-73. PMID: 14615857. https://dx.doi.org/10.1007/s00228-003-0693-0 **KQ1E2, KQ2E2, KQ3E2**
6. Braillon A, Bewley S. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in pregnant women. *Ann Intern Med*. 2016;164(9):637. PMID: 27136221. https://dx.doi.org/10.7326/L15-0625 **KQ1E2, KQ2E2, KQ3E6**
7. Brose LS. Helping pregnant smokers to quit. *BMJ*. 2014;348:g1808. PMID: 24620362. https://dx.doi.org/10.1136/bmj.g1808 **KQ1E2, KQ2E2, KQ3E2**
8. Chan B, Einarson A, et al. Effectiveness of bupropion for smoking cessation during pregnancy. *J Addict Dis*. 2005;24(2):19-23.. PMID: 15784520. https://dx.doi.org/10.1300/J069v24n02_02 **KQ1E2, KQ2E2, KQ3E2**
9. Chen LS, Baker TB, et al. Interplay of genetic risk (CHRNA5) and environmental risk (partner smoking) on cigarette smoking reduction. *Drug Alcohol Depend*. 2014;143:36-43. PMID: 25073833. https://dx.doi.org/10.1016/j.drugalcdep.2014.06.027 **KQ1E2, KQ2E2, KQ3E2**
10. Chun-Fai-Chan B, Koren G, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol*. 2005;192(3):932-6. PMID: 15746694. https://dx.doi.org/10.1016/j.ajog.2004.09.027 **KQ1E2, KQ2E2, KQ3E2**
11. Cole JA, Modell JG, et al. Bupropion in pregnancy and the prevalence of

congenital malformations. *Pharmacoepidemiol Drug Saf*. 2007;16(5):474-84. PMID: 16897811. https://dx.doi.org/10.1002/pds.1296 **KQ1E2, KQ2E2, KQ3E2**

12. Crawford P, Cieslak D. Varenicline for smoking cessation. *Am Fam Physician*. 2017;96(5):Online. **KQ1E2, KQ2E2, KQ3E7**
13. Einarson A, Choi J, et al. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry*. 2009;54(4):242-6. PMID: 19321030. https://dx.doi.org/10.1177/070674370905400405 **KQ1E2, KQ2E2, KQ3E2**
14. Fokina VM, Wang X, et al. Determination of cotinine in the urine of pregnant patients enrolled in a clinical trial for the use of bupropion sustained-release as an aid for smoking cessation. *Drug Alcohol Depend*. 2015;146:e280. https://dx.doi.org/10.1016/j.drugalcdep.2014.09.227 **KQ1E7, KQ2E7, KQ3E3**
15. Gisslen T, Nathan B, et al. Hyperinsulinism associated with gestational exposure to bupropion in a newborn infant. *J Pediatr Endocrinol Metab*. 2011;24(9-10):819-22. PMID: 22145484. **KQ1E2, KQ2E2, KQ3E2**
16. GlaxoSmithKline. The Bupropion Pregnancy Registry: Final Report. 2008. **KQ1E2, KQ2E2, KQ3E2**
17. Gould G, Bovill M, et al. Feasibility and acceptability of ican quit in pregnancy multicomponent implementation intervention and research design for australian indigenous pregnant women: a pilot cluster randomized step-wedge trial. Asia-pacific journal of clinical oncology. Conference: hunter cancer research symposium 2018. Australia. 2018;14(Supplement 6):26-27. https://dx.doi.org/10.1111/ajco.13071 **KQ1E7, KQ2E7, KQ3E4**
18. Gould Gillian S, Bovill Michelle, et al. Feasibility and acceptability of Indigenous Counselling and Nicotine (ICAN) QUIT in pregnancy multicomponent implementation intervention and study design for Australian Indigenous pregnant women: a pilot cluster randomised step-wedge trial. *Addict Behav*. 2019;90:176-190. https://dx.doi.org/http://dx.doi.org/10.1016/j.addbeh.2018.10.036 **KQ1E4, KQ2E4, KQ3**E4
19. Haddad A, Davis AM. Tobacco smoking cessation in adults and pregnant women: behavioral and pharmacotherapy interventions. *JAMA*. 2016;315(18):2011-2. PMID: 27163990. https://dx.doi.org/10.1001/jama.2016.2535 **KQ1E2, KQ2E2, KQ3E7**
20. Harrison-Woolrych M, Paterson H, et al. Exposure to the smoking cessation medicine varenicline during pregnancy: a prospective nationwide cohort study. *Pharmacoepidemiol Drug Saf*. 2013;22(10):1086-92. PMID: 23926076. https://dx.doi.org/10.1002/pds.3489 **KQ1E2, KQ2E2, KQ3E2**
21. Hartmann-Boyce J, Aveyard P. Drugs for smoking cessation. *BMJ*. 2016;352:i571. PMID: 26907501. https://dx.doi.org/10.1136/bmj.i571 **KQ1E2, KQ2E2, KQ3E1**
22. Hegaard HK, Kjaergaard H, et al. Multimodal intervention raises smoking cessation rate during pregnancy. *Acta Obstet Gynecol Scand*. 2003;82(9):813-9. PMID: 12911442. **KQ1E2, KQ2E2, KQ3E4**
23. Hotham ED, Gilbert AL, et al. A randomised-controlled pilot study using nicotine patches with pregnant women. *Addict Behav*. 2006;31(4):641-648. PMID: 15985339. **KQ1E6, KQ2E4, KQ3E6**
24. Janssen R, Oudijk MA. Concerns about the safety of nicotine replacement therapy during pregnancy on lung development in children. *Am J Obstet*

Gynecol. 2017;216(3):327-328. PMID: 27780705. https://dx.doi.org/10.1016/j.ajog.2016.10.023 **KQ1E2, KQ2E2, KQ3E2**

25. Kaplan YC, Olgac Dundar N, et al. Pregnancy outcome after varenicline exposure in the first trimester. *Case Rep Obstet Gynecol.* 2014;2014:263981. PMID: 24639907. https://dx.doi.org/10.1155/2014/263981 **KQ1E2, KQ2E2, KQ3E2**
26. Kapur B, Hackman R, et al. Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. *Curr Ther Res Clin Exp.* 2001;62(4):274-278. **KQ1E4, KQ2E4, KQ3**E2
27. Lancaster T. ACP Journal Club. In pregnant smokers, the nicotine patch did not increase abstinence or birthweight more than placebo. *Ann Intern Med*. 2014;160(12):JC11. PMID: 24935505. https://dx.doi.org/10.7326/0003-4819-160-12-201406170-02011 **KQ1E2, KQ2E2, KQ3E2**
28. Leventhal K, Byatt N, et al. Fetal cardiac arrhythmia during bupropion use. *Acta Obstet Gynecol Scand*. 2010;89(7):980-1. PMID: 20583941. https://dx.doi.org/10.3109/00016349.2010.485632 **KQ1E2, KQ2E2, KQ3E2**
29. Louik C, Kerr S, et al. First-trimester exposure to bupropion and risk of cardiac malformations. *Pharmacoepidemiol Drug Saf*. 2014;23(10):1066-75. PMID: 24920293. https://dx.doi.org/10.1002/pds.3661 **KQ1E2, KQ2E2, KQ3E6**
30. Lusskin SI, Khan SJ, et al. Pharmacotherapy for perinatal depression. *Clin Obstet Gynecol*. 2018;61(3):544-561. PMID: 29561284. https://dx.doi.org/https://doi.org/10.1097/grf.0000000000000365 **KQ1E2, KQ2E2, KQ3E2**
31. Mendelsohn CP. The evidence supports prequit use of nicotine patches. *BMJ*. 2016;353:i2176. PMID: 27090572. https://dx.doi.org/10.1136/bmj.i2176 **KQ1E2, KQ2E2, KQ3E2**
32. Nanovskaya TN, Oncken C, et al. Bupropion sustained release for pregnant smokers: a randomized, placebo-controlled trial. *Am J Obstet Gynecol*. 2017;216(4):420.e1-420.e9. PMID: 27890648. https://dx.doi.org/10.1016/j.ajog.2016.11.1036 **KQ1E6, KQ2E6, KQ3E2**
33. Noonan D, Lyna P, et al. Unintended effects of a smoking cessation intervention on Latino fathers' binge drinking in early postpartum. *Ann Behav Med.* 2016;50(4):622-7. https://dx.doi.org/10.1007/s12160-016-9781-0 **KQ1E8, KQ2E8, KQ3E2**
34. O'Dowd A. Only a tenth of pregnant smokers are prescribed nicotine replacement therapy. *BMJ*. 2014;349:g5405. PMID: 25183700. https://dx.doi.org/10.1136/bmj.g5405 **KQ1E2, KQ2E2, KQ3E2**
35. Olsen M, Petronis KR, et al. Maternal use of varenicline and risk of congenital malformations. *Pharmacoepidemiol Drug Saf*. 2015;24(244). **KQ1E7, KQ2E7, KQ3E2**
36. Palmsten K, Huybrechts KF, et al. Antidepressant use and risk for preeclampsia. *Epidemiology*. 2013;24(5):682-91. PMID: 23873072. https://dx.doi.org/10.1097/EDE.0b013e31829e0aaa **KQ1E2, KQ2E2, KQ3E7**
37. Passey ME, Stirling JM. Evaluation of 'Stop Smoking in its Tracks': an intensive smoking cessation program for pregnant Aboriginal women incorporating contingency-based financial rewards. *Public Health Res Pract.* 2018;28(2):14. https://dx.doi.org/10.17061/phrp2801804 **KQ1E2, KQ2E2, KQ3E8**
38. Richardson JL, Stephens S, et al. Pregnancy outcomes after maternal varenicline use; analysis of surveillance

data collected by the European Network of Teratology Information Services. *Reprod Toxicol*. 2017;67:26-34. PMID: 27851994. https://dx.doi.org/10.1016/j.reprotox.2016.11.010 **KQ1E2, KQ2E2, KQ3E2**

39. Roper L, Tran DT, et al. Algorithm for resolving discrepancies between claims for smoking cessation pharmacotherapies during pregnancy and smoking status in delivery records: the impact on estimates of utilisation. *PLoS One*. 2018;13(8):e0202999. https://dx.doi.org/10.1371/journal.pone.0202999 **KQ1E2, KQ2E2, KQ3E4**
40. Sedgwick P. Controlled trials: allocation concealment, random allocation, and blinding. *BMJ*. 2015;350:h2633. PMID: 25979365. https://dx.doi.org/10.1136/bmj.h2633 **KQ1E2, KQ2E2, KQ3E2**
41. Sedgwick P. Measuring the detriment of treatment: number needed to harm. *BMJ*. 2015;350:h2763. PMID: 26002193. https://dx.doi.org/10.1136/bmj.h2763 **KQ1E2, KQ2E2, KQ3E2**
42. Spindel ER, McEvoy CT. The role of nicotine in the effects of maternal smoking during pregnancy on lung development and childhood respiratory disease. Implications for dangers of e-cigarettes. *Am J Respir Crit Care Med*. 2016;193(5):486-94. PMID: 26756937. https://dx.doi.org/10.1164/rccm.201510-2013PP **KQ1E2, KQ2E2, KQ3E2**
43. Stotts AL, Northrup TF, et al. Randomized, controlled pilot trial of bupropion for pregnant smokers: challenges and future directions. *Am J Perinatol*. 2015;32(4):351-6. PMID: 25111040. https://dx.doi.org/10.1055/s-0034-1386635 **KQ1E2, KQ2E2, KQ3E2**
44. Tappin D, Bauld L, et al. Financial incentives for smoking cessation in pregnancy: randomised controlled trial. *BMJ*. 2015;350:h134. PMID: 25627664. https://dx.doi.org/10.1136/bmj.h134 **KQ1E1, KQ2E1, KQ3E2**
45. Thyagarajan V, Robin Clifford C, et al. Bupropion therapy in pregnancy and the occurrence of cardiovascular malformations in infants. *Pharmacoepidemiol Drug Saf*. 2012;21(11):1240-2. PMID: 23109236. https://dx.doi.org/10.1002/pds.3271 **KQ1E2, KQ2E2, KQ3E2**
46. Wong MK, Barra NG, et al. Adverse effects of perinatal nicotine exposure on reproductive outcomes. *Reproduction*. 2015;150(6):R185-93. PMID: 26432348. https://dx.doi.org/10.1530/REP-15-0295 **KQ1E2, KQ2E2, KQ3E2**

Appendix F Table 1. Population Details From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	Mean age	SES	Race	% Female	Median CPD	Nicotine dependence	Other smoking history	Readiness to quit	Quit history
Bullen, 2013[144] ASCEND Fair	42.4	Marital status: NR Education: 47.3% less than high school Employment: NR Other SES: NR	Maori: 32.4% Non Maori: 67.6%	61.6	17.9	FTND[†] (0 to 10), Median: 5.5 FTND >5: 54.6%	Age of smoking initiation, mean: 15.5 years # years smoking, mean: 24.7 Lives with smokers: 52.1%	Confidence in ability to sustain abstinence (1-5 scale), mean: 3.7 AUTOS Score, mean: 23.0	Past year quit attempt: 55.7%
Caponnetto, 2013[145] ECLAT Fair	44.0	Marital status: NR Education: Low: 31% Intermediate: 53% High: 16% Employment: NR Other SES: NR	NR	36.7	20.0	FTND[†], mean: 5.8	Age of smoking initiation, mean: 16.8 years Packs per year, mean: 24.9 eCO, mean: 20 ppm	NR	Ever attempted to quit: 51% # Lifetime quit attempts, mean: 0.6
Hajek, 2019[154] TEC Fair	41.0	Marital Status: 73.1% Single or divorced/ separated 24.9% married 1.8% widowed Education: 35.3% high school education or less Employment: 69.6% employed Other SES: NR	NR	48.0	15.0	FTND[†], mean: 4.6	Age of smoking initiation, median: 16 years eCO, mean: 20 ppm Has significant other who smokes: 39.1%	NR	Past use for cessation NRT: 74.9% E-cig: 41.5% Varenicline: 33.9% Bupropion: 7.8%

Appendix F Table 1. Population Details From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	Mean age	SES	Race	% Female	Median CPD	Nicotine dependence	Other smoking history	Readiness to quit	Quit history
Lee, 2019[157] Fair	42.3	Marital status: married: 90% unmarried: 10% Education: ≤High school: 60.7 ≥College: 39.3% Employment: 100% Other SES: NE	NR	0	CPD smoked, pack: 1.01 Total smoking amount, pack-year: 21.56	FTND, score: 4.05	Duration of smoking, years: 21.98	Initial confidence about quitting smoking score, 5.95	Number of prior attempts to quit (%): None: 10.0 1: 20.7 ≥2: 69.3
Walker, 2019[155] Fair	41.6	Marital status: NR Education: 35.7% with less than 12 years of education Employment: NR Other SES: NR	Maori: 40.1% Non Maori: 59.9%	68.3	17.3	FTND†, mean: 5.2 Daily smokers: 98.8%	Age of smoking initiation, mean: 15.4 years # of years smoking, mean: 22.6 years Lives with smokers: 41.9%	Motivation to quit,‡ mean score: 3.9 Reduced CPD in past year: 56.4%	Past year quit attempt: 45.1%
Carpenter, 2017[147] Fair	42.2	Marital status: NR Education: 37.1% HS education or less Employment: 54.2% employed (full- or part-time) Other SES: 50.3% income	White: 54.5% African American: 44.0%	60.5	15.3	NR	NR	Motivation to quit (1-10 scale): 4.5	Past year quit attempt: 33.7% Lifetime # quit attempts (mean): 4.2

Appendix F Table 1. Population Details From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	Mean age	SES	Race	% Female	Median CPD	Nicotine dependence	Other smoking history	Readiness to quit	Quit history
		<$25,000							
Cravo, 2016[148] Fair	34.6	Marital status: NR Education: NR Employment: NR Other SES: NR	NR	44.6	5-10 CPD: 34.6% 11-20 CPD: 57.6% 21-30 CPD: 7.8%	FTND[†] Mild: 29.7% Moderate: 55.9% Severe: 14.5%	eCO, mean: 74.8 ppm	Subjects were excluded if they expressed current readiness to quit.	NR
Masiero, 2017[146] Fair	62.8	Marital status: NR Education: NR Employment: NR Other SES: NR	NR	37.1	19.4	FTND[†], mean: 4.3	Age of smoking initiation, mean: 17.4 years eCO, mean: 14.8 ppm	Motivation to quit, mean score (scale 4-19)*: 13	NR
Tseng, 2016[150] Fair	28.9	Marital status: NR Education: 32.7% high school or less Employment: NR Other SES: NR	African American: 29.2% White: 25.0% Other: 8.8% Hispanic of any race: 27.1%	32.7	14.8	Smoking Dependence Mild: 16.3% Moderate: 51.0% Strong to Very Strong: 32.7%	Time to first CPD <=5 min after waking: 25.5% 6–30 min after waking: 42.6% 31–60 min after waking: 21.3% >60 min after waking: 10.6%	Confidence in ability to sustain abstinence (1-10 scale), mean: 6.3 Readiness to quit (1-10 scale), mean: 5.5	Past year quit attempt: 42.9%

*Score of 15 and above indicates high motivation to quit.

[†] Score of 8 or greater indicates high nicotine dependence.

[‡] 1 to 5 point Likert scale where a score of 1 indicates very low motivation to quit and a score of 5 indicates very high motivation to quit.

Abbreviations: ACEND = A study of Cessation using Electronic Nicotine Devices; AUTOS = autonomy over smoking scale; CPD = cigarettes per day; e-cig = electronic cigarette; ECLAT = EffiCacy and safety of an eLectronic cigarette; eCO = expired carbon monoxide; FTND = fagerstrom test of nicotine dependence; NR = not reported; PPM = parts per million; SES = socioeconomic status; TEC = Trial of Electronic Cigarettes

Appendix F Table 2. Intervention and Control Characteristics From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	# of trial arms	Primary e-cig component	Additional intervention components	Behavioral support component description	Number and length of visit(s)	Setting	Delivered intervention details	Adherence
Bullen, 2013[144] ASCEND Fair	3	ARM 1 Elusion e- cigs l with 16 mg/mL nicotine cartridges for 12 weeks Participants received a free e-cig and sufficient nicotine cartridges to last for 4-5 weeks. Participants instructed to use the device exclusively for 12 weeks	ARM 2 NRT (Habitrol 21 mg patches) Participants allocated to patches were sent exchange cards in the mail redeemable for patches from community pharmacies, with instructions to use patches daily, from 1 week before until 12 weeks after their chosen quit day, consistent with smoking cessation guidelines ARM 3 Placebo with 0 mg Elusion e-cigs Participants received free e-cig and cartridges containing 0 mg nicotine labelled in such a way that participants cannot detect if	All participants referred to the New Zealand smoking cessation support helpline for a standardized cessation behavioral support program delivered by trained advisors, with a mini- mum of one follow-up support telephone call over 8–12 weeks. If participants did not want to receive this support, they had access other support services such as 'Txt2Quit' (a mobile phone-based sup- port service), 'QuitCoach' (an internet-based support service), and the 'Quitter's community' (an internet-based blogging forum)	Total #: 4 Baseline visit, and 3 followup visits at months 1, 3 and 6. Visit length: NR	Academic Clinics Research investigator(s)	Participants using both nicotine and placebo e-cigs reported having used an average of 0·7 cartridges per day at 6 months Nicotine patches were used as instructed (an average of one 21mg patch per day) At 6 months, in both the nicotine e-cig and NRT groups, two participants had used bupropion and five had used varenicline in the past month; in the placebo e-cig group, three participants reported using varenicline.	At the 6-month followup, adherence to study treatments was significantly higher in the nicotine e-cig group as compared with the NRT group ($p<0·0001$) and with the placebo e-cig group ($p<0·0001$) 29% (71/ 241) of the nicotine e-cig group and 35% (20 of 57) of the placebo e-cig group persisted with e-cigarette use, with only 8% (17/215) of those in the NRT group still using patches.

Appendix F Table 2. Intervention and Control Characteristics From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	# of trial arms	Primary e-cig component	Additional intervention components	Behavioral support component description	Number and length of visit(s)	Setting	Delivered intervention details	Adherence
			they contain nicotine.					
Caponnetto, 2013[145] ECLAT Fair	3	ARM 1 Categoria e-cig (model 401) with 7.2 mg nicotine cartridges used at will for 12 weeks ARM 2 Categoria e-cig (model 401) with two 6-week supplies of cartridges, one of the 7.2 mg nicotine cartridges and a further 6 weeks with supply of 5.4 mg nicotine cartridges; used at will for 12 weeks total	ARM 3 Placebo with Categoria e-cig (model 401) e-cigs and 12 weeks supply of no-nicotine cartridges	NA	Total #: 9 baseline visit and eight follow up visits at weeks 2, 4, 6, 8, 10, 12, 24 and 52. Visit length: With the exception of the baseline study day, most visits took about 10–15 minutes	Academic Clinics Research investigator(s)	Median cartridge use at 6- and 12-month followup was 0 (IQR 0-2) for the whole cohort and did not differ between study arm	NR
Hajek, 2019[154] TEC Fair	2	One Kit (Aspire) e-cigs with 18mg nicotine cartridges for 52 weeks After the initial 4-week trial period with One Kit cartridges participants were encouraged to experiment with e-	NRT with any type of product (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs) for 52 weeks Use of combinations was	All the participants received the same multisession behavioral support as per U.K. stop-smoking service practice. This support involved weekly one-on-	Total #: 4 Baseline visit, and 3 followup visits at weeks 4, 26, and 52. Visit length: NR	National Health Service (NHS) stop-smoking clinics Primary care physicians and non-clinical research	Most participants in the e-cig group started to purchase their own e-liquids from the first week onwards, with only 7% requesting the second bottle. The mean nicotine content was 18mg/ml, 12mg/ml and 8mg/ml at 4, 26	At 12 months follow-up, 5.7% of EC arm participants reported using non-allocated NRT for at least five consecutive days in the past six months and 22.2% of NRT arm participants

Appendix F Table 2. Intervention and Control Characteristics From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	# of trial arms	Primary e-cig component	Additional intervention components	Behavioral support component description	Number and length of visit(s)	Setting	Delivered intervention details	Adherence
		liquids of different strengths and flavors	encouraged, typically the patch and a faster-acting oral product. Participants were also free to switch product at any time during the follow-up period.	one sessions with local clinicians, who also monitored expired carbon monoxide levels for at least 4 weeks after the quit date		investigators	and 52 weeks, respectively. 88% of NRT arm participants used NRT combinations. This comprised mostly patch plus one of the oral products	reported using non-allocated EC
Lee, 2019[157] Fair	2	ARM 1 E-cigarette (distributed in 12wk supply) ARM 2: Nicotine, gum (distributed in 12wk supply)	e-cigarette (eGO-C Ovale, nicotine 0.01 mg/mL; Janty-Korea Co., Janty-Asia Co., Seoul, Republic of Korea) Nicotine gum (Nicoman, nicotine 2 mg/tablet; Daewoong Pharmaceuticals, Seongnam, Republic of Korea)	50min edu sessions on smoking cessation and the use of smoking-cessation aids were conducted in the medical office where the e-cigarette and nicotine gum were distributed. subjects were instructed to visit the medical office every 4 weeks for evaluation and counseling by an independent health practitioner	Total #: 7 1 50min session at BL; 1 medical office visit (length NR) every 4 wks for 24 wks	Medical (not specified) Subjects were recruited from a motor company	4 (Arm 1) and 14 (Arm 2) withdrew before treatment	NR
Walker, 2019[155] Fair	3	ARM 1 eVOD e-cigarette (2nd gen) starter pack with a supply of 18mg/mL	ARM 2 eVOD e-cigarette (2nd gen) starter pack with a supply of placebo	All groups received moderate-intensity, withdrawal-	Total #: 5 Baseline visit, and 3 followup	Community-based intervention. Patients were recruited from	Use of allocated treatments decreased over time. At 3 months followup, only 50%	In the patch-only group, 15% of the participants crossed over and used e-cigarettes

Appendix F Table 2. Intervention and Control Characteristics From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	# of trial arms	Primary e-cig component	Additional intervention components	Behavioral support component description	Number and length of visit(s)	Setting	Delivered intervention details	Adherence
		nicotine e-liquid cartridges used ad libitum for 14 weeks + NRT (as described in Arm 3)	(no nicotine) e-liquid cartridges used ad libitum for 14 weeks + NRT (as described in Arm 3) Participants randomized to e-cigs were allowed to choose between two preselected flavors of e-liquid in the starter packs, after which both e-cigarette groups were free to seek out new e-cigs and other e-liquids at will ARM 3 NRT with a 21mg, 24-hour nicotine patch (Habitrol); one patch per day for 14 weeks	oriented behavioral support directly following randomization, then once a week for 6 weeks	visits at weeks 4, 12, 24, and 52. Visit length: NR	the general population using national advertising	of participants in all three groups were still using the patch and only 33% of participants randomized to e-cigs were still using their assigned product. At 6 months, only 40% of participants in the patches only group were still using patches and 11% an 13% of participants were using both their allocated patches and ecigs in the nicotine e-cig and no nictotine e-cig groups respectively. Participants only received a median of 3 of the 6 scheduled support calls with participants in ARM 1 receiving more calls than those in ARM 3.	and 11% in the placebo e-cig group reported using nicotine e-cigs
Carpenter, 2017[147]	3	ARM 1 BluCig Starter Pack, with 16	ARM 3 Control group continued	NA	Total #: 7 Baseline	Academic Clinics	44/46 participants randomized to the e-cig group used the	Overall compliance was modest but no

Appendix F Table 2. Intervention and Control Characteristics From Trials of Electronic Cigarettes for Tobacco Cessation

Author, Year Trial name Quality	# of trial arms	Primary e-cig component	Additional intervention components	Behavioral support component description	Number and length of visit(s)	Setting	Delivered intervention details	Adherence
Fair		mg/mL nicotine used at will (with minimal instruction) for 4 months. ARM 2 Midway through the study, the manufacturer of Blu altered the product and discontinued availability of the device, replaced with BluPlus+, with 24 mg/mL nicotine, again offered in both tobacco and menthol flavorings	smoking with conventional cigarettes		visit and 6 follow up visits at weeks 2, 3, 4, 8, 12, and 16. Visit length: NR	Research investigator(s)	e-cig at least once. Most participants reported a high frequency of use during the sampling period (>5 days per week), which decreased to about 3 days per week during follow-up. Over the 21-day sampling period, average duration of e-cig use was 15.4 days among 16 mg e-cig participants and 17.0 days among the 24 mg e-cig group. Just under half (48%) of 24 mg e-cig participants used product all 21 days of the sampling period, versus 30% of 16 mg e-cig participants.	different across groups: 58% of all sessions completed.
Cravo, 2016[148] Fair	2	Prototype e-cig, developed by Fontem Ventures, with 2.7 mg nicotine capsules (menthol or tobacco flavor) for 12 weeks	Control group continued smoking with their own usual conventional cigarette brand for 12 weeks mean ISO	NA	Total #: 8 Baseline visit and 7 followup visits at weeks 1, 2, 4, 6, 8, 10, and 12.	Ambulatory care settings Research investigator(s)	Subjects in the e-cig arm used a mean of 3.29 to 4.15 capsules per day over the study weeks. The mean daily CC use in the CC group	A total of 123 subjects (40.2%) were classified as “EVP- compliant” and 183 (59.8%) were classified as “less-EVP-compliant”. The proportion of EVP-

Appendix F Table 2. Intervention and Control Characteristics From Trials of Electronic Cigarettes for Tobacco Cessation

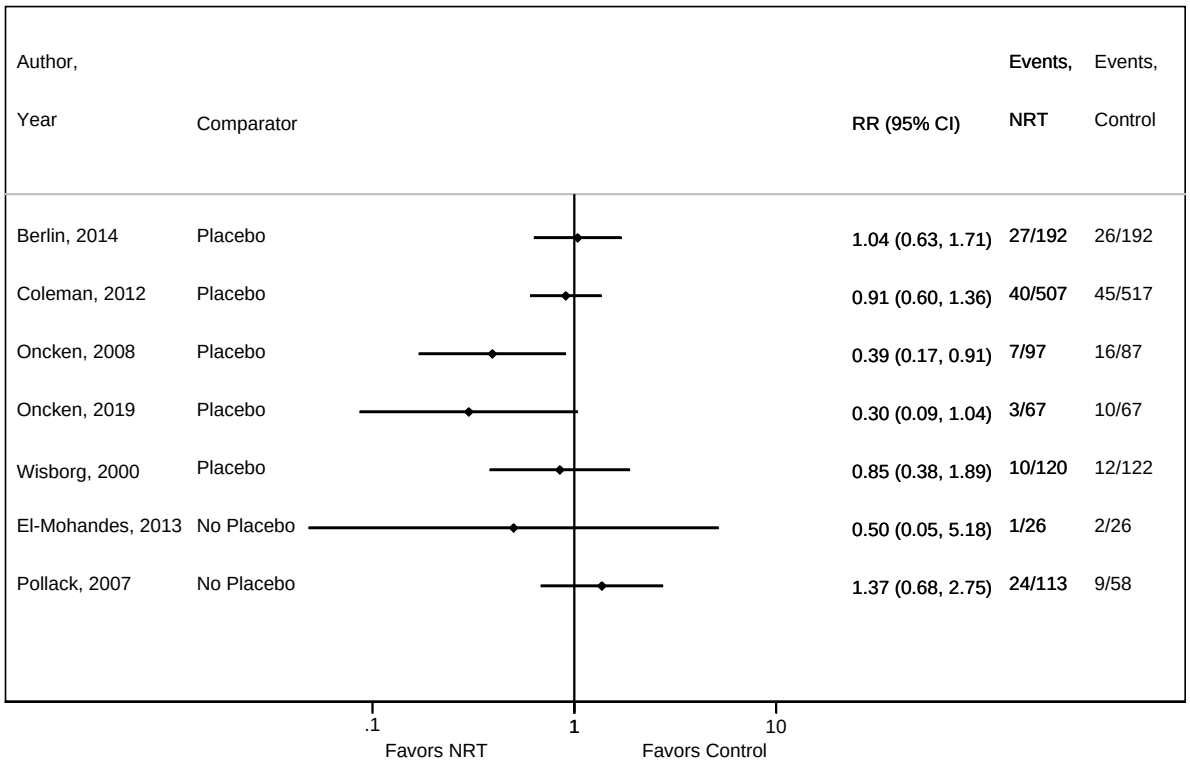
Author, Year Trial name Quality	# of trial arms	Primary e-cig component	Additional intervention components	Behavioral support component description	Number and length of visit(s)	Setting	Delivered intervention details	Adherence
		Participants were provided with the e-cig and with sufficient capsules to last for the duration of the study Each capsule expected to provide 40 to 60 puffs	nicotine yield 0.81 mg and mean ISO tar yield 9.2 mg		Visit length: NR		over the 12 study weeks ranged from 12.33 to 14.1 CPD.	compliant subjects was highest in the subgroup of subjects with lowest CPD consumption at baseline and decreased with increasing CPD at baseline. EVP-compliant subjects did not use more EVP capsules than less-compliant subjects.
Masiero, 2017[146] Fair	3	ARM 1 VP5 e-cig with 8mg nicotine cartridges for 3 months. Each participant received an e-cig kit and 12 10-mL liquid cartridges (8 mg/mL nicotine concentration) free of charge. Participants were asked to consume no more than 1 ml of the liquid a day.	ARM 2 Placebo e-cig with VP5 e-cig Each participant received an e-cig kit and 12 10-mL liquid that did not contain nicotine free of charge. Participants were asked to consume no more than 1 ml of the liquid a day. ARM 3 Behavioral support only	Participants in all arms also received a low-intensity telephone counseling The counselor provided information, supported participants' motivation, and helped them coping with possible roadblocks. The counseling was provided by trained	Total #: 4 Baseline visit, and 3 followup visits at months 1, 2, and 3. Visit length: behavioral counseling was delivered via a 10 min monthly telephone interview. Otherwise NR.	Oncology Clinics	Participants in Arm 3 reported smoking an average of 10.034 cigarettes/day, while participants in Arm 1 and Arm 2 showed a lower consumption (7.671 and 9.091, respectively).	Usage of the e-cig was assessed via a monthly telephone inter-view Participants in Arm 1 and Arm 2 had a similar compliance in the use of e-cigs. And there was no significant difference, though the placebo group used on average less liquid (Arm 1 M = 10.9 empty flacons; Arm 2 M = 9.8 empty flacons).

Appendix F Table 2. Intervention and Control Characteristics From Trials of Electronic Cigarettes for Tobacco Cessation

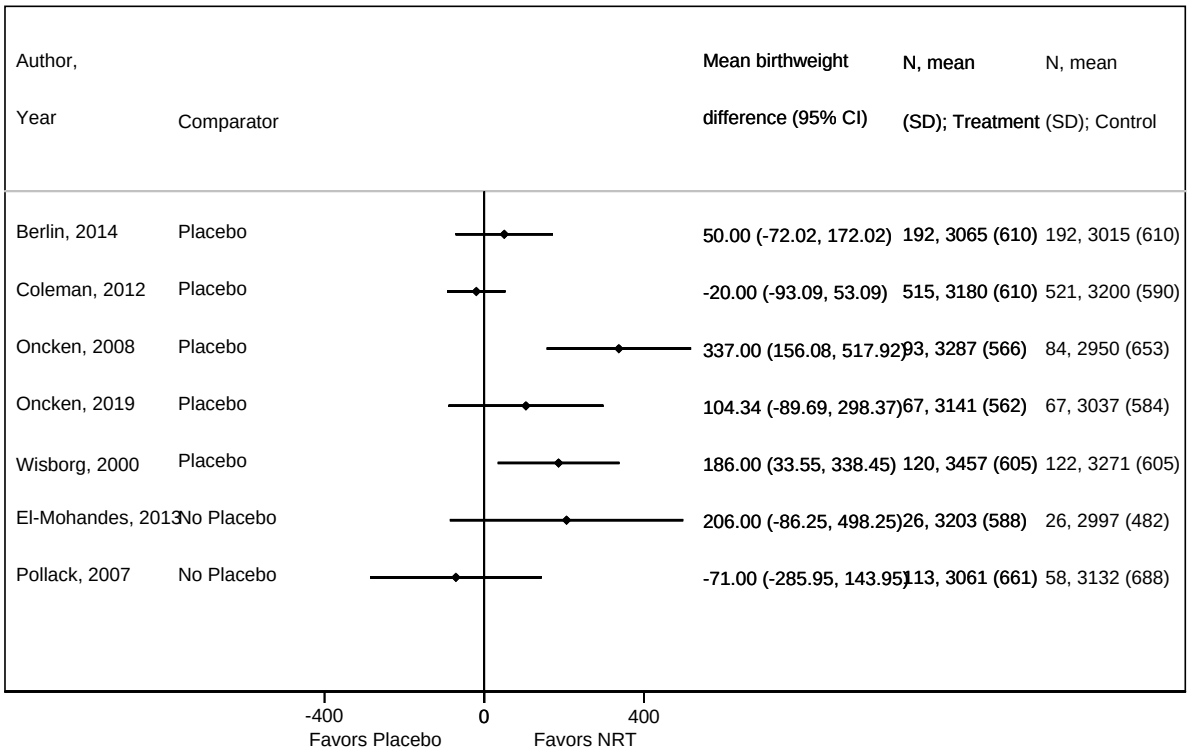
Author, Year Trial name Quality	# of trial arms	Primary e-cig component	Additional intervention components	Behavioral support component description	Number and length of visit(s)	Setting	Delivered intervention details	Adherence
				psychologists.				
Tseng, 2016[150] Fair	2	ARM 1 NJOY, King Bold disposable e-cigs with 4.5% nicotine (tobacco flavor only) for 3 weeks ARM 2 Placebo with no-nicotine NJOY, King Bold disposable e-cigarettes (tobacco flavor only) for 3 weeks Minimum EC use instruction was provided	NR	Prior to receiving the ECs, subjects were required to complete a counseling session with a trained tobacco cessation counselor to review current smoking patterns and offer behavioral change strategies. These included specific smoking reduction options and other strategies to manage urges	Total #: 3 Baseline visit, and 2 followup visits at weeks 1 and 3. Visit length: NR, but counseling visit was 20-30 min in length	Ambulatory care settings Research investigator(s)	NR	NR

Abbreviations: ACEND = A study of Cessation using Electronic Nicotine Devices; CC = conventional cigarettes; CPD = cigarettes per day; e-cigs = electronic cigarettes; ECLAT = EffiCacy and safety of an eLectronic cigarette; NR = not reported; TEC = Trial of Electronic Cigarettes

Appendix G Figure 1. NRT Interventions for Smoking Cessation During Pregnancy, Preterm Birth at <37 Weeks

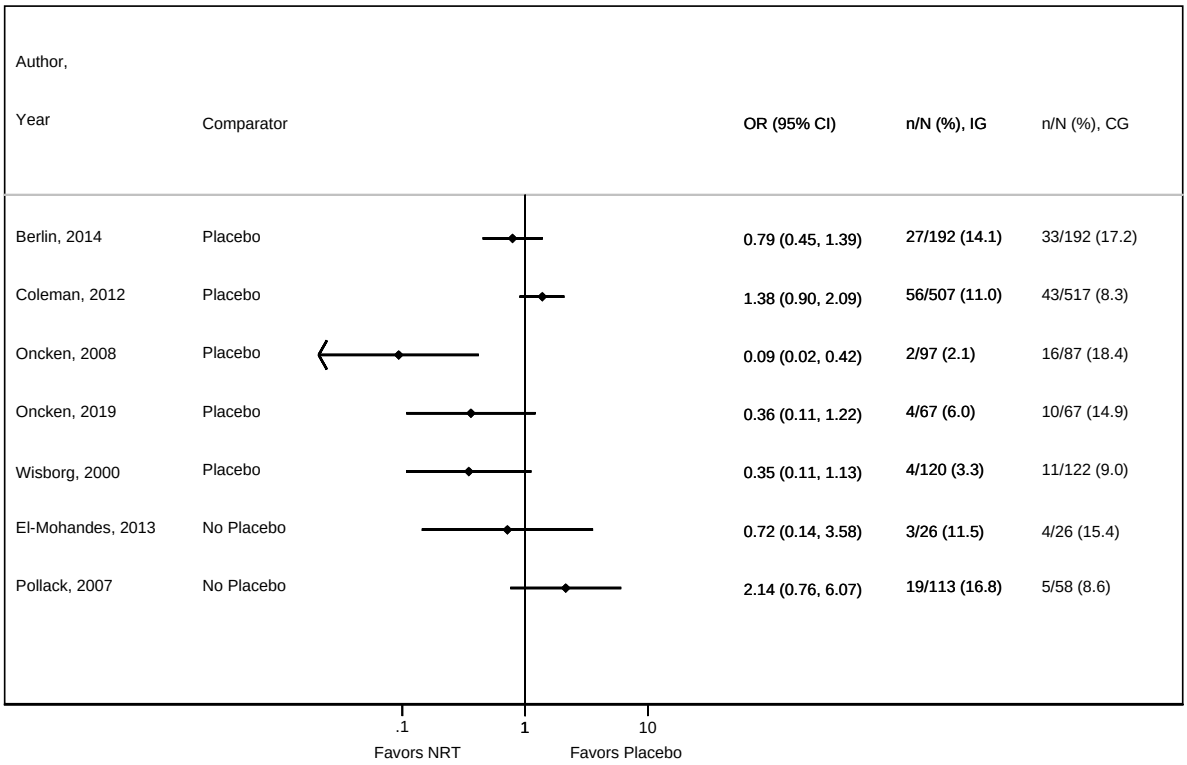


Appendix G Figure 2. NRT Interventions for Smoking Cessation During Pregnancy, Mean Birthweight in Grams



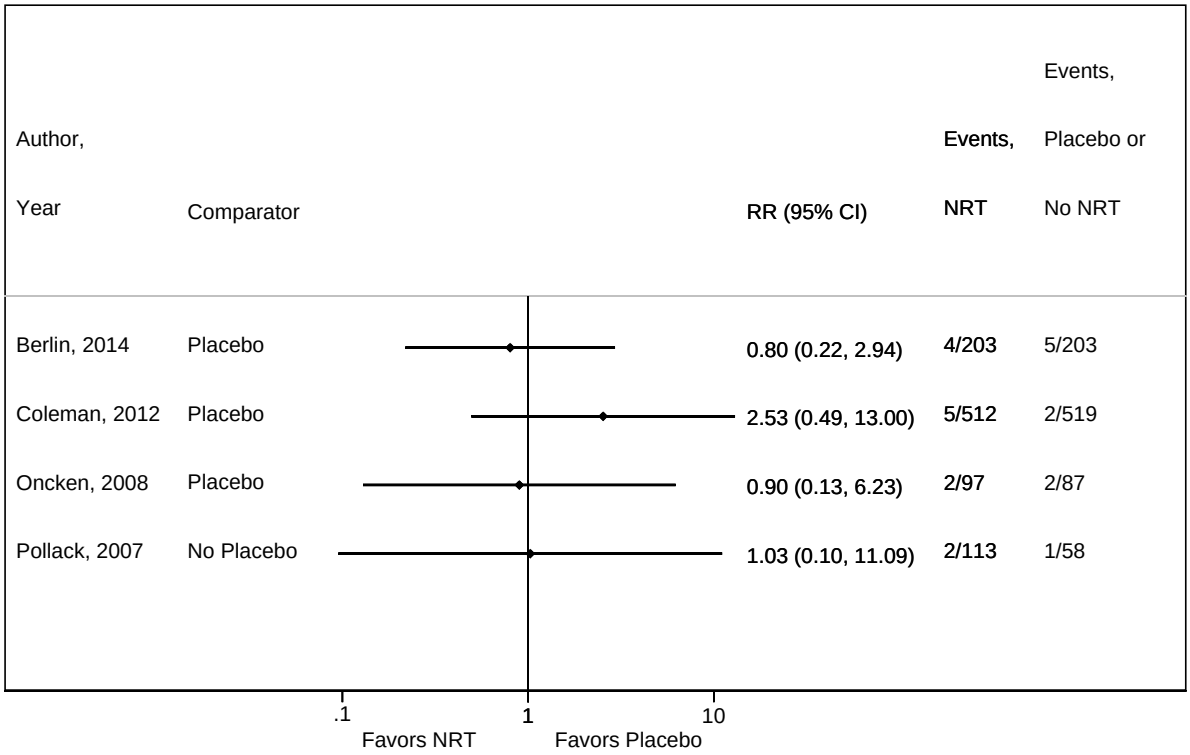
NOTE: Standard deviations for Wisborn, 2000 and El-Mohandes, 2013 abstracted from review by Claire et. al, 2020.[76]

Appendix G Figure 3. NRT Interventions for Smoking Cessation During Pregnancy, Low Birthweight (<2500 Grams)*

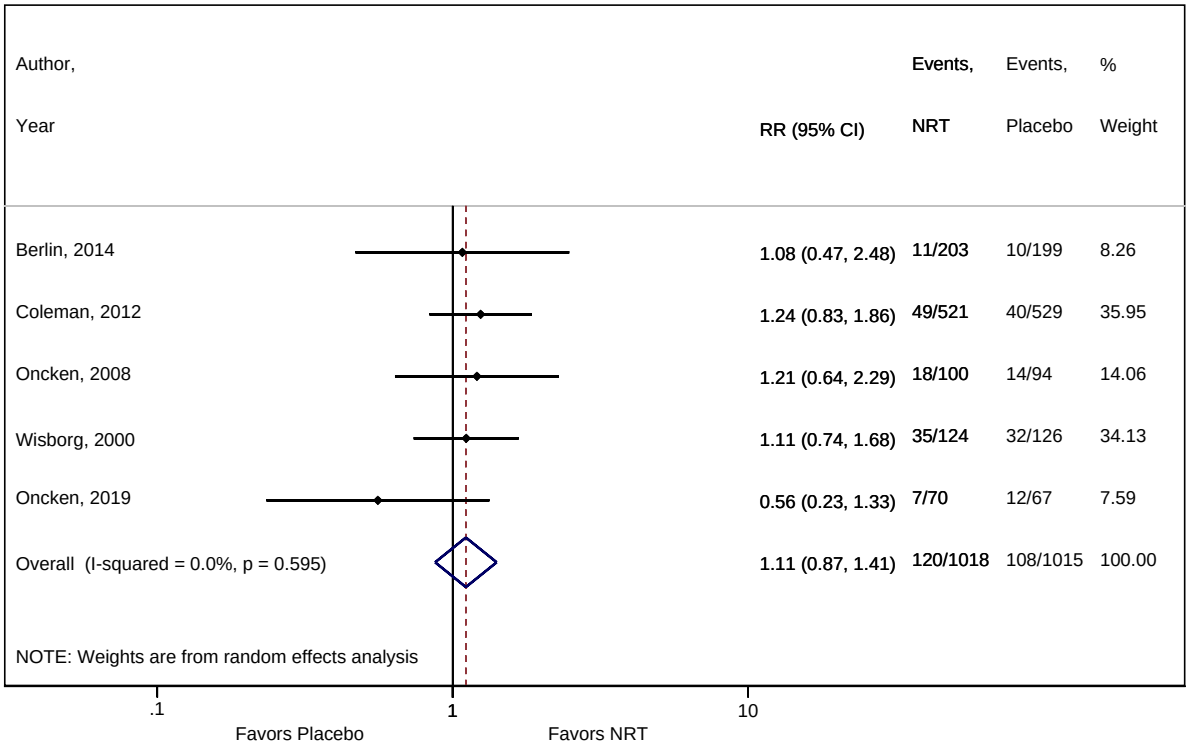


NOTE: Study reported odds ratios were used when reported in original publication.

Appendix G Figure 4. NRT Interventions for Smoking Cessation During Pregnancy, Stillbirth



Appendix G Figure 5. NRT Interventions in Placebo-Controlled Trials for Smoking Cessation During Pregnancy, Smoking Cessation (KQ 2)



NOTE: Pooled estimate from REML with Knapp-Hartung modification: RR= 1.11 (95% CI 0.79 to 1.56)

Appendix G Table 1. Population Details From NRT Trials for Smoking Cessation Among Pregnant Women

Author, Year Trial name Quality	Mean age	Weeks' gestation at BL, mean (range)	SES (%)	Race (%)	OB & medical Hx (%)	Median CPD and Nicotine dependence	Readiness to quit	Quit Hx
Berlin, 2014[167] SNIPP Good	29.3*	NR (9-12 week's gestation)	Married*†: 85 Edu: NR Employment*: Employed: 57 Housewife: 22 Unemployed or Student: 21 Other 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	European: 95 African: 3	Nulliparous*: 27.9 Hx of Premature birth(s)*: 9.5 Hx of small gestational age*: 10.7 Other medical: Maternal Disorders before randomization*: 9.5	10.5* Fagerstrom test (0 to 10), Median: 4.5 (IQR 3-6)	Participants were required to have scored at least a 5 on a motivational scale (range 0-10)	Previous quit attempts (≥ 1 week): 1 (IQR 0-2)
El-Mohandes, 2013[171] Fair	27.5*	18.5 (<30 weeks' gestation)	Married†: 12 Edu: <HS degree: 33 HS graduate‡: 50 At least some college: 17% Employment: Full time: 17 Part-time: 13 Not employed: 69 Other SES: Medicaid (%): 96	African American: 100	Nulliparous: NR Hx of Premature birth(s): NR Hx of small gestational age: NR Other medical: Pregnancies (+current), mean: 5.6 Number of live births, mean: 2.4 Alcohol use during pregnancy: 16	Mean # CPD <7days: 6.0 Nicotine dependence: NR	NR	NR

Appendix G Table 1. Population Details From NRT Trials for Smoking Cessation Among Pregnant Women

Author, Year Trial name Quality	Mean age	Weeks' gestation at BL, mean (range)	SES (%)	Race (%)	OB & medical Hx (%)	Median CPD and Nicotine dependence	Readiness to quit	Quit Hx
					(31%) Any depressive symptoms: 31 (60%) Marijuana during pregnancy: 12 (235)			
Coleman, 2012[168] SNAP Good	26.3*	16.3 (12-24 weeks' gestation)	Married*: NR Edu*: NR Employment: NR Other SES: NR Mean age at leaving full-time education, yrs*: 16.3	White British*: 97.0	Nulliparous*: 0-1: 68.5 Hx of Premature birth(s)*: 8.8 Hx of small gestational age*§: NR Other medical: Use of NRT within pregnancy and prior to enrollment*‖ (%): 4.5	14 Nicotine dependence: NR	NR	NR
Oncken, 2008[174] Fair	25.1	17.1 (≤26 weeks' gestation)	Married†: 30 Edu: <HS grad: 50 HS grad: 33.5 Employment: 33 Other SES (%): Public Insurance: 83 Private Insurance: 17	Non-Hispanic White: 35 Non-Hispanic Black: 30 Hispanic: 54 Other: 3%	Nulliparous: 16.5 Hx of Premature birth(s): 15 Hx of small gestational age: NR Other medical (%): Average number of pregnancies: 3 Methadone maintenance: 6.5	Mean # CPD, last 7 days: 9.45 Mean Fagerstrom scores: 3.55 (IQR 1.93)	NR	Number of previous quit attempts: 2.79

Appendix G Table 1. Population Details From NRT Trials for Smoking Cessation Among Pregnant Women

Author, Year Trial name Quality	Mean age	Weeks' gestation at BL, mean (range)	SES (%)	Race (%)	OB & medical Hx (%)	Median CPD and Nicotine dependence	Readiness to quit	Quit Hx
					Antidepressant use: 7.5% Mental health Tx Hx: 41.5% Substance abuse Tx Hx: 18.5%			
Oncken, 2019[175] Fair	27.6	17.5 (13-26 weeks' gestation)	Married: NR Edu: HS Grad: 19 College or post-college completed: 16 Other SES (%): Public Insurance: 63.5 Private Insurange: 5	White: 25.5 Black: 11.1 Hispanic: 30.4 Other: 0.5	Nulliparous: 13 Hx of premature delivery: 10.6 Hx of SGA: NR Other medical: Hx of depression or anxiety: 41.6% Substance abuse: 24.5% Progesterone use: 5.5% No of previous (median) pregnancies: 2	Mean CPD: 8.4 Mean Fagerstrom test score: 4.3	Motivation to quit (0-10): 8.4	NR
Pollak, 2007[176] Baby Steps Fair	27	18 (13-25 weeks' gestation)	Married†: 30 Edu: <HS grad: 28 HS grad‡: 31 College degree or higher: 5 Employment: Full-time: 67 Part-time: 17 Unemployed: 67 Other SES:	White: 69 Black: 24 Other: 8	Nulliparous: 16 Hx of Premature birth(s)*: 15 Hx of small gestational age*: 5 Other medical: Number of prior pregnancies median (median, IQR): 2 (1,4) Premature rupture	Mean CPD: 11 (5) Nicotine dependence mean (SD): 3 (1)	"Desire to quit" Mean: 6 (1)	Quit at least 24 hours during this pregnancy: 28%

Appendix G Table 1. Population Details From NRT Trials for Smoking Cessation Among Pregnant Women

Author, Year Trial name Quality	Mean age	Weeks' gestation at BL, mean (range)	SES (%)	Race (%)	OB & medical Hx (%)	Median CPD and Nicotine dependence	Readiness to quit	Quit Hx
			NR		of membranes: 7% High blood pressure: 19% Prior history of miscarriage, ectopic pregnancy, or stillbirth: 50%			
Wisborg, 2000[178] Fair	28.4	NR (<22 weeks' gestation)	Married*†: 76.5 Edu: Years of schooling*: <10: 18.4 ≥ 10: 66.8 Missing: 14.8 Employment: Employed*: 51 Other SES: NR	NR	Nulliparous: 42.8 Hx of Premature birth(s): NR Hx of small gestational age: NR Other medical: Alcohol intake (drinks/wk)*: 0–2: 87.5% ≥3: 9% Missing: 11%	Mean CPD: 13.8 Mean Fagerstrom score: Listed but no data provided	NR	Previous attempts to quit, %* 0-2: 68.8 3-15: 31.2

* Calculated
† Married includes married or cohabitating
‡ HS graduate or GED
§ Defined as any previous pregnancy which lasted from 24 to 37 week
‖ The median number of days before recruitment that women last used NRT among the 47 women who reported current or past use was 31 days for the NRT group (IQR 15 to 38 days) and 30 for the placebo group (IQR 14 to 68 days).

Abbreviations: BL = baseline; CPD = cigarettes per day; HS = high school; hx= history; IQR = interquartile range; NR = not reported; SES = socioeconomic status; Tx = treatment; yrs = years

Appendix G Table 2. Intervention Characteristics From NRT Trials for Smoking Cessation Among Pregnant Women, by Study Design

Author, Year Trial name Quality	NRT component	Behavioral component description	Number and length of visit(s)	Setting Provider	Delivered intervention details	Adherence
Berlin, 2014[167] SNIPP Good	NRT, patch 10 mg and 15 mg; 16 hour delivery nicotine patches	Behavioral support. Participants received behavioral support at each visit. Although the personalized, individual behavioral interventions were not specifically standardized, and the participating maternity wards could use their discretion to apply their own standard methods, these interventions were based on the national consensus document. The study's website along with flyers in waiting rooms provided information that participants would receive personalized (not within groups) interventions by healthcare professionals specialized in smoking cessation. The core feature of the behavioral interventions included motivational interviewing, arrangement for follow-ups, behavioral counselling, establishment of good doctor-patient and midwife-patient relationships, and a clear definition of treatment aims.	Total #: 7 Initial visit 1hr, following visits at least 10min	Maternity ward Research investigator(s)	Daily dose ranged from 10-30 mg/day Mean daily prescription dose for entire tx period IG: 18mg (SD 6.8mg), CG: 19.2 (SD 6.9mg). Median length of prescription was: IG: 105 days (IQR 35-175), CG: 70 (IQR 35-175) In total, 21,722 nicotine patches and 19,702 placebo patches were issued to the participants	Compliance was recorded among 307 (76%) participants at 1016 visits, self-reported. Compliance assessed in 164/203 (81%) women in the nicotine patch group and 143/199 (72%) in the placebo patch group. The median self-reported compliance rate was 85% (interquartile range 56-99%) in the nicotine patch group and 83% (56-95%) in the placebo patch group. Completed all visits: IG: 96/203 (47.3%), CG: 76/199 (38.2%)
Coleman, 2012[168] SNAP Good	Active nicotine patches 15 mg per 16 hours (4wk supply, additional 4wk supply if needed)	Behavioral counseling (1 face-to-face and 3 telephone sessions). At enrollment, research midwives provided behavioral support lasting up to 1 hour. In addition to behavioral support at enrollment, research midwives	Total #: 4 (1 initial + 3 phone); +1 additional face-to-face for women still smoking after	OBGYN, clinical Research midwives	Gum usage ranged from about 90% usage at visit 1 to 30% usage at visit 5. Number of days of	At delivery, only 7.2% (35/485) of IG and 2.8% (14/496) CG reported using trial medications for over 1 month.

Appendix G Table 2. Intervention Characteristics From NRT Trials for Smoking Cessation Among Pregnant Women, by Study Design

Author, Year Trial name Quality	NRT component	Behavioral component description	Number and length of visit(s)	Setting Provider	Delivered intervention details	Adherence
		provided three sessions of behavioral support by telephone to participants: one session on the quit date, one session 3 days afterward, and one at 4 weeks. The women who collected a second month's supply of NRT or placebo also received face-to-face support from the research midwife at the time of collection. Women were offered additional support from local National Health Service smoking cessation services and were encouraged to ask for support from the research midwives or smoking cessation service staff; support was provided according to the manual.	1mo. Initial visit up to 1hr; phone visits NR		gum use [placebo: 29.9 (SD=3.4); NRT: 37.8 (SD=3.8)] Average number of pieces of gum used per day [placebo: 3.22 (SD=2.27); NRT: 3.04 (SD=2.43)]	Rates of use of nonstudy nicotine-replacement therapy were very low. Most participants had no additional contact, either face to face or by text message, with smoking-cessation advisors. Median number of extra phone contacts: 2 in each group.
Oncken, 2008[174] Fair	Nicotine gum 2mg; 6 weeks of treatment with the gum followed by a 6-week taper period.	Behavioral counseling (8 face-to-face sessions). At BL and Visit 1, women received individualized smoking cessation counseling. Subjects received two 35-minute counseling sessions (in English or Spanish) delivered by a research assistant trained to deliver smoking cessation counseling using a motivational interviewing approach. In addition to the counseling sessions, subjects received printed educational materials that were tailored for use in pregnancy and twice-monthly telephone calls to monitor progress until delivery.	Total #: 8 35 min (2 visits); NR for phone or other visits.	NR Study Nurse (dispensed medication); Smoking cessation therapist; Research assistants	Initial session: lasted an average 64.7 minutes (SD15.8): CBT-only, 61.7, (16.7); and CBT+NRT, 66.1, (15.7). Sessions two through six lasted an average 25.7 minutes (SD14.1): CBTonly, Mean 23.6min, (10.7); and CBT+NRT: M27.0 min, (13.9). CBT+NRT (n=122): 72 selected the patch, 32 selected the	Overall, the IG was more likely to attend study visits than the placebo group (71% vs. 60%; t(10)= 3.67, p=.004). The nicotine group participated at a significantly higher rate at visits 3 ($\chi2(1)= 5.26$, p=.022) and 5 ($\chi2(1)= 4.74$, p=.029) and at the postpartum visit ($\chi2(1)= 4.47$, p=.035).

Appendix G Table 2. Intervention Characteristics From NRT Trials for Smoking Cessation Among Pregnant Women, by Study Design

Author, Year Trial name Quality	NRT component	Behavioral component description	Number and length of visit(s)	Setting Provider	Delivered intervention details	Adherence
					gum, 12 selected the lozenge, and 6 opted to use no NRT. Mean of 40 patches dispatched, however, women reported using a mean of only 23.4 patches Gum dispensed to last the women 18 days; they reported using gum for 8 days Lozenges dispensed to last 19 days; the women reported using lozenges for a mean of 4 days Overall, 76% of the women in the CBT+NRT arm reported using some form of NRT Only four women in the CBT-only arm reported using NRT	

Appendix G Table 2. Intervention Characteristics From NRT Trials for Smoking Cessation Among Pregnant Women, by Study Design

Author, Year Trial name Quality	NRT component	Behavioral component description	Number and length of visit(s)	Setting Provider	Delivered intervention details	Adherence
Oncken, 2019[175] Fair	NRT, inhaler (4mg of nicotine from a porous plug containing 10mg of nicotine) Planned for 6 wks; inhaler available for additional 6wks if the participant was abstinent from smoking. Number of inhalers used per day based on level of smoking.	Protocol consisted of nine in-person visits and a phone call one month after delivery. After randomization, at the next two visits (baseline and one week after the quit date) participants received 35 minutes of individual smoking cessation counseling by a study nurse who was trained to deliver the counseling using a motivational interviewing approach. At the baseline visit we asked participants to pick a quit date (a date that they would completely stop smoking beginning at 12 am) sometime within the next week and to start using the inhaler on that date. We also provided written educational materials on smoking cessation during pregnancy and the package insert for the nicotine inhaler.	Total #: 10 (9 in-person, 1 phone) Length of visits: NR	NR Study nurse	NR	Compliance with the inhaler during treatment was 69% in the placebo group and 70% in the nicotine group, which was not significant (p>0.99).
Wisborg, 2000[178] Fair	NRT, patch (15 mg/ 16 hrs for 8 weeks, 10 mg/16 hrs for 3 weeks) planned for 11 weeks.	Behavioral counseling (4 visits). Prenatal smoking cessation counseling with a midwife four times during pregnancy. Visits were independent of routine antenatal care visits. At first visits, which lasted 45–60 minutes, participants were interviewed about their smoking habits and previous attempts to stop smoking. Women were informed about pharmacologic and psychologic aspects of smoking and the consequences of smoking during pregnancy. Methods to stop smoking were carefully explained and the day of stopping was planned. A pamphlet on smoking and pregnancy also was distributed; pamphlets contained	Total #: 4 Initial visit: 45-60min; remaining 3 lasted 15-20 min	NR Study midwife	NR	In the nicotine group 17% used all 15-mg patches and 11% used all 10-mg patches. In the placebo group 8% and 7% used all patches.

Appendix G Table 2. Intervention Characteristics From NRT Trials for Smoking Cessation Among Pregnant Women, by Study Design

Author, Year Trial name Quality	NRT component	Behavioral component description	Number and length of visit(s)	Setting Provider	Delivered intervention details	Adherence
		information about the harmful effects of smoking and gave brief advice on smoking cessation				
El-Mohandes, 2013[171] Fair	Trans-dermal NRT, 14-21mg for 10 wks depending on CPD	Behavioral counseling (5 face-to-face and 1 telephone session) Delivery of an evidenced-based intervention: the Smoking Cessation or Reduction in Pregnancy Treatment (SCRIPT) Program. In addition to counseling, women were given A Pregnant Woman's Guide to Quit Smoking, a manual to assist patients with problem-solving and coping skills, written at a 6th grade reading level. Women who continued after visit 1 received reinforcement and behavioral methods at Visits 2–5.	Total #: 6 (max) Varied: "Frequency of contact and total time with each patient was standardized"	Clinical, private room Intervention specialists	Majority received between 31-60min (82%), 15.7% received <30min, and 2.3% received over 60min behavioral support	Sixty-five percent of patients completed the NRT protocol. CG patients were adherent to the scheduled counseling and assessment visits. Although adherence levels in the IG and CG were comparable for Visit 1 to 4, the NRT Implementation Index was much lower for Visit 5 and 6.
Pollak, 2007[176] Baby Steps Fair	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) Each woman's NRT dose was based on current smoking level: Overall	All women received six one-on-one counseling sessions (five face-to-face at prenatal visits and one via telephone) designed to enhance motivation and develop skills needed to quit smoking. "Quit kit" given: a smoking cessation booklet designed for pregnant smokers (Make Yours a Fresh Start Family), water bottle, straws, hard candy, an exercise band, and a stress management tape. Support specialists helped the women devise an action plan. After the first session, each woman was mailed a card containing details of her action plan. In	Total #: NR Length: NR	Clinical (prenatal visits), 1 phone Support specialist (Behav)	The median number of patches used was 14 (range 0–77) in the nicotine group and 7 (range 0–77) in the placebo group Women who did not attend visits were given another appointment within the subsequent 2 weeks. If they did	A greater proportion of the women in the CBT+NRT arm completed four or more sessions (four was median number of sessions) than did women in the CBT-only arm (70% vs 53%, p=0.02, RD=0.17, 95% CI0.10–0.24).

Appendix G Table 2. Intervention Characteristics From NRT Trials for Smoking Cessation Among Pregnant Women, by Study Design

Author, Year Trial name Quality	NRT component	Behavioral component description	Number and length of visit(s)	Setting Provider	Delivered intervention details	Adherence
	encouraged to use NRT for 6wks.	all sessions, support specialists attempted to increase the women's motivation, self-efficacy, and skills. In addition to the smoking-specific content, support specialists covered a relevant content area (stress, rewards, social support, and relapse prevention). The counseling protocol was based on motivational interviewing, the transtheoretical model of behavior change, and social cognitive theory.			not attend again they were contacted by telephone. At second, third, and fourth visits, 76 (31%), 106 (44%), and 129 women (53%), respectively, were telephoned.	

Abbreviations: BL = baseline; CBT = cognitive behavioral therapy; CG = control group; CI = confidence interval; CPD = cigarettes per day; IG = intervention group; mg = milligram; min = minute(s); NR = not reported; NRT = nicotine replacement therapy; OBGYN = obstetrics and gynecology; RCT = randomized controlled trial; RD = risk difference; SES = socioeconomic status; Tx = treatment; wks = weeks; yrs = years

Appendix H Table 1. Intervention Details of Behavioral Interventions Among Adults

Intervention Type	Physician or nurse advice	Individual or group-based counseling	Telephone and mobile phone-based interventions
Primary population	Adult smokers who were typically motivated to quit, including generally healthy smokers as well as those with specific health needs such as those with smoking-related diseases and people with mental illness.		
Primary outcomes measured	Smoking cessation at the longest followup (at 6 months or more) using the strictest definition of abstinence, preferring sustained over point prevalence abstinence and using biochemically validated rates where available.		
Study findings	Physician and nurse advice can increase the rate of smoking cessation at 6 or more months followup (RR for physician advice 1.76 [95% CI, 1.58 to 1.96]; 26 trials; n=22,239 and for nurse advice 1.29 [95% CI, 1.21 to 1.38]; k=44; n=20,881).	Individual counseling from a smoking cessation specialist increases the rate of cessation among smokers at 6 or more months followup versus no advice, brief advice, or self-help materials (RR 1.48 [95% CI, 1.34 to 1.64]; k=33; n=13,762) and moderate quality evidence that compared with non-group self-help programs, group-based therapy interventions can increase quitting smoking (RR 1.88 [95% CI, 1.52 to 2.33]; k=13; n=4395).	Providing proactive telephone counselors after smokers have called a Quitline improves rates of smoking cessation (RR 1.38 [95% CI, 1.19 to 1.61]; k=14; n=32,484), and moderate quality evidence that proactive telephone counseling increases quit rates in smoking in other settings (RR 1.25 [95% CI, 1.15 to 1.35]; k=65; n=41,233). Mobile phone-based interventions were less commonly studied but showed a positive benefit on smoking cessation at 6 months' followup compared with usual care or a minimal intervention (RR 1.54 [95% CI, 1.19 to 2.00]; k=13; n=14,133) and no intervention (RR 1.59 [95% CI, 1.09 to 2.33]; k=4; n=997).
Behavior change goals and techniques	Advice was defined as verbal instructions from the provider with a "stop smoking" message irrespective of whether information was provided about the harm effects of smoking; however, the included interventions were highly variable. In most cases, advice was given verbally and was supplemented with print materials, additional advice from additional healthcare staff, or referral to a cessation clinic.	Typically included: review of smoking history and motivation to quit, help in the identification of high-risk situations, and the generation for problem-solving strategies to deal with such situations as well as non-specific support and encouragement. Many group-based sessions included cognitive behavioral therapy. Additional components such as written materials, video or audiotapes were also sometimes provided.	Telephone counseling and mobile phone-based interventions were generally tailored according to participants' smoking history, readiness to quit and focused on increasing motivation and strategies to increase likelihood of quitting.
Duration of interventions	Most interventions took place during 1 session with followup between 1 week and 3 months.	Most interventions took place during one face-to-face session with followup consultations over 1 week to 4 months followup.	Highly variable ranging from 2 weeks to 1 year with most taking place over 3 to 4 months.
Settings of studies	Most took place in primary care or hospital settings.	Most took place in hospital or smoking cessation clinic settings.	Most interventions were delivered entirely remotely via telephone or mobile phone, with few providing any face-to-face support.
To whom is intervention targeted?	Adult smokers motivated to quit.	Adult smokers, regardless of motivation to quit.	Generally adult smokers motivated to quit. Most mobile phone-based interventions targeted younger- (mean age 18-27 years) or middle-aged adults (up to mean age of 45 years).
Mode and intensity of delivery	Most advice was given during a single consultation lasting less than 20 minutes (with or without print materials) plus up to one followup visits; although several studies compared more intense interventions (more than one session) with minimal interventions.	Most individual-based advice was given during one face-to-face session with multiple followup sessions in-person or via the telephone. Group-based sessions included smokers meeting for scheduled meetings delivered over 6 to 8 sessions, with the first few sessions devoted to	Telephone counseling was typically delivered in scheduled phone calls that began after smokers had proactively called a smoking Quitline. The number of calls ranged from a single call to 12 calls. The duration of the calls was typically 10 to 20 minutes, although the first calls were often

Appendix H Table 1. Intervention Details of Behavioral Interventions Among Adults

Intervention Type	Physician or nurse advice	Individual or group-based counseling	Telephone and mobile phone-based interventions
		discussion of motivation for quitting, health benefits, and strategies for planning a quit attempt.	longer. Almost all the included trials of mobile phone-based interventions used text messaging (SMS) as a central component of the intervention. The number of text messages varied considerably but often was 0 to 2 messages per day every day over the course of the intervention.
Example interventions[*] [†]	Morgan 1996[§1] Canga 2000[§2]	Fiore 2004[3] Glasgow 2000[4] Weissfeld 1991[§5]	Bock 2013[8] Curry 1995[9] Ellerbeck 2009[6] McBride 1999[10] McClure 2005[7] Orleans 1991[§11] Rigotti 2006[12]
Materials provided for practice[†] [**]	Treatment guide: Orleans CT, Rimer BK, Fleisher L. Clear horizons: a quit smoking guide especially for those 50 and over. Philadelphia: FoxChase Cancer Center, 1989. (Morgan 1996[1]) Intervention based on protocols established in How to Help Your Patients Stop Smoking: A National Cancer Institute Manual for Physicians[13] and followed the orientation of the Mayo Nicotine Dependence Center[14] (Canga 2000[2])	Office of Cancer Communications. Clearing the Air: How to Quit Smoking and Quit for Keeps. Bethesda, Md: National Cancer Institute; 1987. (Weissfeld 1991[5])	American Lung Association guide (Bock 2013[8]) Curry, S.J., Gordon, J. R., & Marlatt, G. A. (1987). Breaking Away: A guide to becoming a nonsmoker; unable to find original materials. (Curry 1995[9]) https://www.cancer.gov/publications/patient-education/clearing-the-air (McBride 1999[10]) American Lung Association maintenance manual (American Lung Association. (1980). A lifetime of freedom from smoking. New York: Author) (Orelans 1991[11]) Solomon L, Quinn V. Spontaneous quitting: self-initiated smoking cessation in early pregnancy. Nicotine Tob Res 2004;6 suppl:S203–16. (Rigotti 2006[12])
Evidence of effect modification	There was insufficient evidence to establish differences according to the intensity of the intervention. There was some evidence that physician advice interventions that provided further followup to a minimal intervention vs. those delivered in one single session were more effective, but this effect was not seen related to nurse advice. There was no evidence that the effects differed by patient group or setting.	No evidence of effect modification based on whether pharmacotherapy was offered nor on population (hospital inpatients or outpatients vs. not). Evidence was too limited to determine whether there was a dose-response effect according to number of contacts or type (face-to-face vs. remote) of followup consultations.	Some evidence that participants who were selected based on their motivation to quit may be more likely to quit smoking versus those who were not selected on their motivation in response to proactive telephone counseling. There was not enough evidence to suggest that a higher number of calls would result in a larger effect. There were minimal differences in the effectiveness of mobile phone-based interventions according to different population and intervention characteristics.
Comparison group	No advice or usual care.	No advice, brief advice, self-help materials, or usual care; non-group-based interventions.	No intervention, self-help materials, or other nontailored and noninteractive remote support.
Interventionist	Physicians (e.g., general practitioners, family	Smoking cessation specialists often with	Telephone counseling was most often provided by

Appendix H Table 1. Intervention Details of Behavioral Interventions Among Adults

Intervention Type	Physician or nurse advice	Individual or group-based counseling	Telephone and mobile phone-based interventions
and training required	practice) or nursing staff with or without smoking-related duties as part of their core clinical duties. Information about training provided to staff was not synthesized and was rarely reported. In those reporting, training ranged from "brief tutorial" to a 4-hour training.	backgrounds in social work, psychology, psychiatry, health education, and nursing. Training was otherwise not described.	professional counselors or trained health care professionals. Many text message-based interventions were developed and administered through computer expert generated systems.
Reported adherence to intervention	Adherence to intervention not synthesized or abstracted by reviews.		

* Example interventions are those that demonstrated a positive direction of effect on smoking cessation, were at low risk-of-bias, and took place in the United States in primary care or a primary care-applicable setting among an unselected sample of adults (i.e., those not selected based on having smoking-related disease or other co-morbid conditions)
† Inclusion of studies and materials are for example purposes only and does not indicate endorsement by the USPSTF.
** Materials provided for practice include materials or protocols that were noted within the source study and that we were able to locate.
§ Statistically significantly effect of intervention versus control on smoking cessation at 6 months or more followup.

[1]Morgan GD, Noll EL, Orleans CT, et al. Reaching midlife and older smokers: tailored interventions for routine medical care. Prev Med. 1996;25(3):346-54. 10.1006/pmed.1996.0065
[2]Canga N, De Irala J, Vara E, et al. Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. Diabetes care. 2000;23(10):1455-60. 10.2337/diacare.23.10.1455
[3]Fiore MC, McCarthy DE, Jackson TC, et al. Integrating smoking cessation treatment into primary care: an effectiveness study. Prev Med. 2004;38(4):412-20. 10.1016/j.ypmed.2003.11.002
[4]Glasgow RE, Whitlock EP, Eakin EG, et al. A brief smoking cessation intervention for women in low-income planned parenthood clinics. Am J Public Health. 2000;90(5):786-9. 10.2105/ajph.90.5.786
[5]Weissfeld JL, Holloway JL. Treatment for cigarette smoking in a Department of Veterans Affairs outpatient clinic. Arch Intern Med. 1991;151(5):973-7.
[6]Ellerbeck EF, Mahnken JD, Cupertino AP, et al. Effect of varying levels of disease management on smoking cessation: a randomized trial. Ann Intern Med. 2009;150(7):437-46.
[7]McClure JB, Westbrook E, Curry SJ, et al. Proactive, motivationally enhanced smoking cessation counseling among women with elevated cervical cancer risk. Nicotine Tob Res. 2005;7(6):881-9. 10.1080/14622200500266080
[8]Bock B, Heron K, Jennings E, et al. A Text Message Delivered Smoking Cessation Intervention: The Initial Trial of TXT-2-Quit: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2013;1(2):e17. 10.2196/mhealth.2522
[9]Curry SJ, McBride C, Grothaus LC, et al. A randomized trial of self-help materials, personalized feedback, and telephone counseling with nonvolunteer smokers. J Consult Clin Psychol. 1995;63(6):1005-14.
[10]McBride CM, Scholes D, Grothaus LC, et al. Evaluation of a minimal self-help smoking cessation intervention following cervical cancer screening. Prev Med. 1999;29(2):133-8. 10.1006/pmed.1999.0514
[11]Orleans CT, Schoenbach VJ, Wagner EH, et al. Self-help quit smoking interventions: effects of self-help materials, social support instructions, and telephone counseling. J Consult Clin Psychol. 1991;59(3):439-48.
[12]Rigotti NA, Park ER, Regan S, et al. Efficacy of telephone counseling for pregnant smokers: a randomized controlled trial. Obstet Gynecol. 2006;108(1):83-92. 10.1097/01.AOG.0000218100.05601.f8
[13]Glynn TJ, Manley MW: How to Help Your Patients Stop Smoking: A National Cancer Institute Manual for Physicians. Washington, DC, U.S. Govt. Printing Office, 1998 (DHHS publ. no. 98-3064)
[14]Hurt RD, Dale LC, McClain FL, Eberman KM, Offord KP, Bruce BK, Lauger GG: A comprehensive model for the treatment of nicotine dependence in a medical setting. Med Clin North Am 76:495–514, 1992

Appendix H Table 2. Intervention Details of Behavioral Interventions Among Pregnant Women

Intervention Type	Individual psychosocial interventions
Primary population	Generally healthy pregnant adult women over 16 years of age, but including those with specific health needs. About half of the included trials explicitly recruited women categorized as having low socioeconomic status.
Primary outcomes measured	Smoking cessation in late pregnancy and continued abstinence post-partum. Using the strictest definition of abstinence, preferring sustained over point prevalence abstinence and using biochemically validated rates where available.
Study findings	Psychosocial interventions among pregnant women increased the rate of smoking cessation in late pregnancy compared with control (RR 1.35 [95% CI, 1.23 to 1.48]; 97 trials; n=26,637).
Behavior change goals and techniques	Psychosocial interventions were defined as non-pharmacological strategies that use cognitive behavioral, motivational and supportive therapies to help women to quit. This included counselling, health education, feedback, financial incentives, social support from peers and/or partners, and exercise, as well as dissemination trials.
Duration of interventions	Most interventions recruited women during their first antenatal visit or second trimester of pregnancy; the duration of the intervention typically took place from this time until late pregnancy.
Settings of studies	Most interventions took place in women's clinics or tobacco cessation clinics.
To whom is intervention targeting?	Pregnant women who are currently smoking or have recently quit smoking.
Mode and intensity of delivery	Smoking cessation interventions implemented during pregnancy differed substantially in their intensity, their duration, and the people involved in their implementation.
Example interventions*†	Bullock 2009[1] Lee 2015[2] Pollack 2013[3] Stotts 2009[4] Windsor 2011[5]
Materials provided for practice†**	All patients (both control and experimental groups) received (Ask-Advise-Assess-Arrange) SCRIPT Procedures 1, 2, 3, 9, and 10.[6, 7, 8, 9] and experimental group patients also received Assist SCRIPT Procedures 4 through 8, which included a video,[10] guide to quit smoking,[11] and a 10 minute or less counseling session[12]
Evidence of effect modification	Meta regression analyses found no differences in the effects of behavioral interventions according to the specific intervention strategies, comparator, intensity (categorized according to frequency of contact), intervention duration, the provision of self-help manuals, including telephone support, the SES of the sample, newly added studies, or study design (cluster versus individually randomized trials).
Comparison group	Any control
Interventionist and training required	Varied
Reported adherence to intervention	Adherence to intervention not synthesized by review.

* Example interventions are those that demonstrated a positive direction of effect on smoking cessation, took place in the United States in primary care or a primary care-applicable setting, and were published in the past 10 years

Appendix H Table 2. Intervention Details of Behavioral Interventions Among Pregnant Women

[†] Inclusion of studies and materials are for example purposes only and does not indicate endorsement by the USPSTF.
[**] Materials provided for practice include materials or protocols that were noted within the source study and that we were able to locate.

[1]Bullock L, Everett KD, Mullen PD, et al. Baby BEEP: A randomized controlled trial of nurses' individualized social support for poor rural pregnant smokers. Matern Child Health J. 2009;13(3):395-406. 10.1007/s10995-008-0363-z

[2]Lee M, Miller SM, Wen KY, et al. Cognitive-behavioral intervention to promote smoking cessation for pregnant and postpartum inner city women. J Behav Med. 2015;38(6):932-43. 10.1007/s10865-015-9669-7

[3]Pollak KI, Lyna P, Bilheimer A, et al. A pilot study testing SMS text delivered scheduled gradual reduction to pregnant smokers. Nicotine Tob Res. 2013;15(10):1773-6. 10.1093/ntr/ntt045

[4]Stotts AL, Groff JY, Velasquez MM, et al. Ultrasound feedback and motivational interviewing targeting smoking cessation in the second and third trimesters of pregnancy. Nicotine Tob Res. 2009;11(8):961-8. 10.1093/ntr/ntp095

[5]Windsor R, Woodby L, Miller T, et al. Effectiveness of Smoking Cessation and Reduction in Pregnancy Treatment (SCRIPT) methods in Medicaid-supported prenatal care: Trial III. Health Educ Behav. 2011;38(4):412-22. 10.1177/1090198110382503

[6]Fiore, M.; Bailey, W.; Cohen, S., et al. Smoking cessation: clinical practice guideline. Rockville, MD: AHCPR; 1996.

[7]Fiore, M.; Bailey, W.; Cohen, S., et al. Treating tobacco use and dependence: a clinical practice guideline. Rockville, MD: AHRQ; 2008.

[8]Windsor R, Cutter G, Morris J, Reese Y, Manzella B, et al. The effectiveness of smoking cessation methods for smokers in public health maternity clinics: A randomized trial. American Journal of Public Health. 1985; 75:1389–1392.

[9]Windsor R, Lowe J, Perkins L, et al. Health education for pregnant smokers: Its behavioral impact and cost benefit. American Journal of Public Health. 1993; 83:201–206.

[10]Windsor, R.; Crawford, M.; Woodby, L. Commit to quit smoking during and after pregnancy. Washington, DC: 1998. [Video]. UAB Medical Television. Edited 2004, Society for Public Health Education, www.sophe.org.

[11]Windsor, R. A Pregnant Woman's Guide to Quit Smoking. ISBN 0-935105-01-08. Washington, DC: Society for Public Health Education; 1985 &2005. www.sophe.org.

[12]Laine C, Davidoff F. The patient-physician relationship: Patient-centered medicine, a professional evolution. Journal of the American Medical Association. 1996; 275:152–156.

Appendix I Table 1. Ongoing or Recently Completed Studies: Electronic Cigarettes

Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	Status (Sep 2020)
NCT03453385 Matthew Carpenter	Clinical Outcomes of a Nationwide, Naturalistic E-Cig Trial (CONNECT)	USA	660	2-arm smoking cessation trial for 6 months comparing (1) e-cigarettes (2) continued smoking with conventional cigarettes	7-day PPA at 6 months	Recruiting: Est completion date July, 2022.
NCT03511001 Kim Pulvers	Effects Among Smokers Who Use and Do Not Use E-Cigarettes	USA	187	2-arm smoking cessation trial comparing (1) 6 weeks of JUUL e-cigarettes vs. (2) 6 weeks of smoking as usual	Blood pressure outcomes Respiratory symptoms	Active, but not recruiting: Est completion date December, 2019; No results published.
NCT04084210 Megan Piper	Understanding the Real-World Impact of the Use of Three Alternate Nicotine-Delivery Products on Combustible Cigarette Use	USA	200	3-arm smoking cessation trial comparing: 1) Very low nicotine cigarettes (VLNCs); 2) Juul e-cigarettes; or 3) no alternative product. During two different weeks, participants will be asked to switch from their usual cigarettes and use only study products. They will also be asked to use either an active nicotine or placebo patch (the within-subjects factor), provided in double-blind fashion and counterbalanced order.	Number of conventional cigarettes smoked during each Switch Week Number of VLNCs or **JUUL** pods used during each Switch Week	Not yet recruiting: Est. completion date March, 2022.
NCT03743532 Darla Kendzor	Preliminary Evaluation of Alternative Approaches to Combustible Cigarette Cessation (Exchange Project Sub-Study)	USA	60	3-arm smoking cessation trial among low SES persons comparing 1) incentives for quitting smoking in addition to combination nicotine replacement therapy (patches + lozenges), 2) the provision of JUUL(device and pods) along with directions to switch over from combustible cigarettes to	CO-verified 7-day PPA at 1 month	Not yet recruiting: Est. completion date December, 2020.

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Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	Status (Sep 2020)
				e-cigarettes exclusively, or 3) the combination of JUULand incentives for combustible cigarette cessation.		
ACTRN12612001210864 Coral Gartner	Can using nicotine as a long-term substitute enhance smoking cessation over using it only as a cessation aid?	Australia	1600	Combination of varying levels of self-help materials, NRT, advice, or e-cigarettes	Continuous abstinence at 6 months 7-day PPA at 6 months	Completed in December, 2015. No results available.
NCT02417467 Mark Eisenberg and Andréa Hébert-Losier	Evaluating the Efficacy of E-Cigarette Use for Smoking Cessation (E3) Trial	Canada	486	3-arm smoking cessation trial with 12 weeks intervention and observation up to 12 months comparing (1) Nicotine e-cigarettes plus minimal behavioral counseling with (2) placebo e-cigarettes plus minimal behavioral counseling and (3) minimal behavioral counseling only	Continuous abstinence verified by exhaled-CO<11ppm at 6 and 12 months 7-day PPA verified by exhaled-CO<11ppm at 6 and 12 months Incidence of adverse events/serious adverse events at 3 months	Active, not recruiting: Est completion date December, 2020 Protocol published May 2020 Presented by Dr. Mark J. Eisenberg at the American College of Cardiology Virtual Annual Scientific Session Together With World Congress of Cardiology (ACC 2020/WCC), March 30, 2020
NCT03249428 Smita Pakhal	E-Cigarette Inner City RCT	Canada	200	2-arm smoking cessation trial for 12 months comparing (1) NRT plus behavioral counseling with (2) e-cigarettes plus behavioral counseling	7-day PPA (validated) at 6 and 12 months Quality of life at 6 months	Not yet recruiting: Est completion date September, 2021

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Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	Status (Sep 2020)
NCT03235505 Tuula Toljamo	Efficacy and Safety of E-cigarettes for Smoking Cessation in Middle-aged Heavy Smokers (EFFECT)	Finland	450	3-arm smoking cessation trial with 12 weeks intervention and observation up to 12 months comparing (1) Nicotine e-cigarettes + placebo-pills + Motivational Interview (MI) with (2) Placebo e-cigarettes + varenicline + MI and (3) Placebo varenicline + placebo e-cigarettes + MI	7-day point prevalence abstinence (PPA) verified by exhaled-CO<10ppm at 12 months	Recruiting: Est completion date December, 2020
NCT03630614 Ivan Berlin	Randomized Trial of Electronic Cigarettes with or Without Nicotine in Smoking Cessation (ECSMOKE)	France	650	3-arm smoking cessation trial for 6 months comparing (1) use of nicotine e-cigarettes plus placebo varenicline tablets with (2) placebo e-cigarettes plus active varenicline and (3) placebo e-cigarettes plus placebo varenicline	7-day PPA at 6 months Incidence of adverse events at 6 months	Recruiting: Est completion date March, 2022
NCT01979796 Pasquale Caponnetto	Antismoking Effects of Electronic Cigarettes in Subjects with Schizophrenia and Their Potential Influence on Cognitive Functioning (SCARIS)	Italy	153	3-arm smoking cessation trial among persons with schizophrenia for 3 months (1) nicotine e-cigarettes with (2) Placebo e-cigarettes and (3) no-nicotine inhalers	Continuous abstinence verified by exhaled-CO≤7ppm at 12 months	Not yet recruiting: Est completion date December, 2021
NCT02124187 Eugenio Aguglia	Smoking Cessation and Reduction in Depression (SCARID)	Italy	129	3-arm smoking cessation trial among persons with depression for 3 months comparing (1) nicotine e-cigarettes with (2) Placebo e-cigarettes and (3) no-nicotine inhalers	Continuous abstinence verified by exhaled-CO≤7ppm at 12 months	Not yet recruiting: Est completion date June, 2022
NCT03589989 Reto Auer and Anna Schöni	Electronic Nicotine Delivery Systems (ENDS/Vaporizer/E-cigarette) as an Aid for Smoking Cessation (ESTxENDS)	Switzerland	1,172	2-arm smoking cessation trial for 6 months comparing (1) e-cigarettes plus behavioral counseling with (2) behavioral counseling only	Continuous abstinence verified by urinalysis and exhaled-CO at 6 months	Recruiting: Est completion date December, 2021

Appendix I Table 1. Ongoing or Recently Completed Studies: Electronic Cigarettes

Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	Status (Sep 2020)
					7-day PPA at 6 months validated by urinalysis Incidence of adverse events and withdrawal symptoms at 6 months Chemical toxin levels at 6 months Change in depressive symptoms, metabolism, stress levels, respiratory symptoms, and sleep quality at 6 months	
NCT04236791 Reto Auer and Anna Schöni	The ESTxENDS Trial-Electronic Nicotine Delivery Systems as an Aid for Smoking Cessation-extension of Follow-up (ESTxENDS)	Switzerland	1,172	2-arm smoking cessation trial for 24 months comparing (1) e-cigarettes plus behavioral counseling with (2) behavioral counseling only	Continuous abstinence verified by urinalysis or exhaled-CO at 12, 24 months 7-day PPA at 12, 24 months validated by urinalysis or exhaled-CO Incidence of adverse events and withdrawal symptoms at 12,	Recruiting: Est completion date June, 2023

Appendix I Table 1. Ongoing or Recently Completed Studies: Electronic Cigarettes

Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	Status (Sep 2020)
					24 months Use of any other smoking cessation products at 12, 24 months Health-related quality of life, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression at 12, 24 months	
NCT03061253 Markos Klonizakis	E-cigarettes and Cardiovascular Function (ISME-NRT)	England	249	3-arm smoking cessation trial for 3 months comparing (1) nicotine-inclusive e-cigarettes (2) nicotine-free e-cigarettes (3) nicotine Replacement Therapy (NRT)	Intervention effect on Total Cholesterol/LDL ratio at 6 months	Active, not recruiting: Est completion date Nov 2020; No results published.
NCT04251273 Amanda L Graham	Text Message Quit Vaping Intervention for Young Adults	USA	2900	2-arm vaping cessation trial for 6 months comparing (1) text message-based intervention for quit vaping support and (2) assessment only	30-day self-reported PPA at 7 months	Active, not recruiting: Est completion date January, 2021.

Appendix I Table 2. Ongoing or Recently Completed Studies: Pharmacotherapy in Pregnant Women

Study reference/ trial identifier Primary investigator	Study name	Location	Estimated n	Description	Status (Sep 2020)
NCT01656733 Cheryl Oncken	Nicotine Replacement for Smoking Cessation During Pregnancy	US	154	Pregnant smokers who smoke at least 5 cigarettes/ day will receive nurse-delivered behavioral counseling and be randomized to receive a 6-week course of treatment with either a nicotine inhaler or placebo, followed by a 6-week taper.	Completed: Results submitted to clinical trials but not publicly available. No publication available.
NCT02188459 Henry Kranzler	Placebo-controlled Trial of Bupropion for Smoking Cessation in Pregnant Women (BIBS)	US	360	A randomized, parallel-group, double-blinded, placebo-controlled, 10 week trial of Bupropion in 360 pregnant women who smoke daily and wish to quit smoking.	Completed: No results posted; no publication available.
NCT03819231 David Black	Mindfulness Training Plus Oxytocin (MOXY)	US	180	Clinical trial aimed to examine the effects of mindfulness training and a single 40 IU dose of Pitocin (oxytocin, USP; concentration = 10 IU/1 mL; PAR Pharmaceuticals, NY, USA) on smoking.	Recruiting: Est completion date Dec 2023.
NCT03480373 Cheryl Oncken	Electronic Cigarette Use During Pregnancy	US	375	Observational study aimed to compare overall toxicant exposure in pregnant women who use e-cigs with women who smoke conventional cigarettes. Will also compare toxicant exposure and birth outcomes among infants born to pregnant women who use e-cigs compared to women who smoke conventional cigarettes.	Suspended: Est completion date: May 2023.
NCT01290445 Pfizer	Varenicline Pregnancy Cohort Study	Denmark, Sweden	Actual enrollment: 885,185	A prospective population-based cohort study 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.	Completed May 2016: Results available on clinicaltrials.gov; no publication available.
ACTRN12618000576224 Adrian Dunlop	Targeted antenatal smoking cessation intervention in high-risk substance dependent pregnancy: a feasibility study	Australia	100	This study aims to assess the feasibility and acceptability of the addition of current evidence-based smoking cessation care to routine prenatal care of women attending a substance use in pregnancy clinic.	Recruiting: Anticipated date of last data collection January, 2020. Protocol published Nov 2019.

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Study reference/ trial identifier Primary investigator	Study name	Location	Estimated n	Description	Status (Sep 2020)
ACTRN12615001278527 Sue Kildea	Assessment of the acceptability, feasibility and impact on smoking cessation, of an intensive smoking cessation intervention, including financial incentives, among pregnant Indigenous women reporting daily smoking and receiving maternity care through the Birthing in Our Community program.	Australia	140	This study will assess how effective the program is, what women think about it, and how easy it is to provide "Stop Smoking in its Tracks". The study will involve collecting information on the care provided, whether women quit smoking and what other factors might be influencing quit attempts and successful quitting.	Recruiting: Anticipated date of last data collection Jun 2019; no results published.

Abbreviations: EST = estimated; mg = milligram(s); UK = United Kingdom; US = United States