REVIEW

Annals of Internal Medicine

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

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

Background: Tobacco use is the leading cause of preventable death in the United States.

Purpose: To review the effectiveness and safety of pharmacotherapy and behavioral interventions for tobacco cessation.

Data Sources: 5 databases and 8 organizational Web sites were searched through 1 August 2014 for systematic reviews, and PubMed was searched through 1 March 2015 for trials on electronic nicotine delivery systems.

Study Selection: Two reviewers examined 114 articles to identify English-language reviews that reported health, cessation, or adverse outcomes.

Data Extraction: One reviewer abstracted data from good- and fair-quality reviews, and a second checked for accuracy.

Data Synthesis: 54 reviews were included. Behavioral interventions increased smoking cessation at 6 months or more (physician advice had a pooled risk ratio [RR] of 1.76 [95% CI, 1.58 to 1.96]). Nicotine replacement therapy (RR, 1.60 [CI, 1.53 to 1.68]), bupropion (RR, 1.62 [CI, 1.49 to 1.76]), and varenicline (RR, 2.27 [CI, 2.02 to 2.55]) were also effective for smoking cessation. Combined behavioral and pharmacotherapy interventions increased cessation by 82% compared with minimal intervention or usual care (RR, 1.82 [CI, 1.66 to 2.00]). None of the drugs were associated with major cardiovascular adverse events. Only 2 trials addressed efficacy of electronic cigarettes for smoking cessation and found no benefit. Among pregnant women, behavioral interventions benefited cessation and perinatal health; effects of nicotine replacement therapy were not significant.

Limitation: Evidence published after each review's last search date was not included.

Conclusion: Behavioral and pharmacotherapy interventions improve rates of smoking cessation among the general adult population, alone or in combination. Data on the effectiveness and safety of electronic nicotine delivery systems are limited.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2015;163:608-621. doi:10.7326/M15-0171 **www.annals.org**
For author affiliations, see end of text.
This article was published online first at www.annals.org on 22 September 2015.

Cigarette smoking and exposure to smoke result in more than 480 000 premature deaths in the United States every year, along with substantial illness (1, 2). Despite considerable progress in tobacco control over the past 50 years, in 2013, an estimated 17.8% of U.S. adults (3) and 15.9% of pregnant women aged 15 to 44 years were current cigarette smokers (4). Many tools are available to help smokers quit, including counseling by health care providers, telephone- and print-based interventions, computer and text-messaging interventions, and pharmacologic agents (that is, nicotine replacement therapy [NRT], bupropion hydrochloride sustained release [bupropion], and varenicline).

In 2009, the U.S. Preventive Services Task Force (USPSTF) reaffirmed its 2003 recommendation that clinicians ask all adults about tobacco use and provide interventions for cessation for those who use tobacco products (grade A recommendation) (5). The original USPSTF recommendation (2003) and reaffirmation (2009) were based on the Public Health Service's clinical practice guidelines on treating tobacco use and dependence (6, 7). Because there were no plans to update the Public Health Service report, we undertook the current review to assess the benefits and harms of behavioral and pharmacologic interventions for tobacco cessation in adults, including pregnant women, to assist the USPSTF in updating its 2009 recommendation. Because of the rapid increase in the use of electronic nicotine delivery systems (ENDS) and the vigorous debate about the public health effect of these devices and their role in smoking cessation (8–13), our review also synthesized the primary trial evidence on the efficacy and safety related to this technology as a means for quitting conventional smoking.

See also:

Related article 622

Methods

We relied primarily on a review of reviews method for this update. We did not replicate quality rating or data abstraction for original studies or replicate review-specific analyses. However, we decided a priori to conduct a de novo search for primary evidence related to the effectiveness and safety of ENDS. In addition, we did a bridge search for evidence related to pharmacotherapy interventions among pregnant women because of the limited number of studies included in the available systematic reviews and the length of time that had elapsed since their last search dates.

We developed an analytic framework and 3 key questions with input from the USPSTF (Appendix Figure 1, available at www.annals.org). The final version of the framework and key questions reflects both USPSTF and public input. The full report provides detailed methods (14).

Data Sources and Searches

We searched the following databases for relevant reviews from January 2009 to 1 August 2014: PubMed, PsycInfo, Cochrane Database of Systematic Reviews, Health Technology Assessment database, and Database of Abstracts of Reviews of Effects of the Centre for Reviews and Dissemination. We also searched the following organizational Web sites: the Agency for Healthcare Research and Quality, the *British Medical Journal Clinical Evidence* (through 7 August 2013), the Canadian Agency for Drugs and Technologies in Health, Guide to Community Preventive Services, the Institute of Medicine, the National Institute for Health and Clinical Excellence, the National Health Service Health Technology Assessment Programme, and the Surgeon General. We supplemented our searches with suggestions from experts. We searched PubMed for primary evidence related to ENDS through 1 March 2015 and for pharmacotherapy interventions among pregnant women through 15 August 2014 (the full report outlines the search strategies for these 2 searches [14]).

Study Selection

Two investigators independently reviewed all identified abstracts and dually reviewed full-text articles against prespecified eligibility criteria (14). We resolved disagreements through discussion. We included systematic reviews—with or without meta-analysis—that examined the effectiveness of interventions for tobacco cessation for adults, including pregnant women, and were linked to primary care or took place in a general adult population. We excluded nonsystematic meta-analyses and narrative reviews. We also excluded reviews that focused on reduction of tobacco harms, interventions for relapse prevention, or cessation medications that were not approved by the U.S. Food and Drug Administration as first-line medications for cessation (such as nortriptyline). We included only the most recent version of updated reviews. We outlined separate selection criteria when considering primary evidence related to ENDS and pharmacotherapy among pregnant women, as described in the full report (14).

Data Extraction and Quality Assessment

At least 2 independent reviewers rated the quality of all included systematic reviews using a slightly modified version of the Assessment of Multiple Systematic Reviews tool (15, 16) (see the full report for modifications and methods for determining the overall quality rating of individual reviews [14]). We excluded all poor-quality studies (17). One reviewer completed primary data abstraction, and a secondary reviewer checked all data for accuracy and completeness.

Data Synthesis and Analysis

When we found several fair- and good-quality reviews that met the inclusion criteria in a given population and intervention subgroup, we applied criteria (Appendix Table 1, available at www.annals.org) to identify 1 or more reviews that represented the most current and applicable evidence to serve as the basis for the main findings (called "primary reviews"). We reviewed the remaining reviews for complementary or discordant findings. When we encountered discordant bodies of evidence, we sought explanations for these differences by examining the eligibility criteria and included studies within each review.

We used the pooled point estimates presented in the included reviews when appropriate. We did not reanalyze any of the individual study evidence. We evaluated the appropriateness of meta-analytic procedures and used our technical judgment to interpret pooled analyses accounting for limitations or concerns around heterogeneity, statistical approaches (18, 19), and other factors.

Role of the Funding Source

This review was funded by the Agency for Healthcare Research and Quality. Agency staff provided technical oversight for the project. Liaisons from the USPSTF helped resolve issues around the review's scope but were not involved in its conduct.

RESULTS

We reviewed 638 abstracts and 114 full-text reviews for possible inclusion (Appendix Figure 2, available at www.annals.org). We identified 54 systematic reviews that met our eligibility criteria (20–73), and 22 of these served as the basis for the primary findings (Table 1). In general, results across all included reviews were consistent within each population and intervention grouping. Our results are organized by outcomes and subcategories by population and interventions. Eleven of the 54 included reviews synthesized evidence on interventions among specific subpopulations of adults (such as persons with depression and young adults) that are not included here but appear in detail in the full report (14).

Behavioral Interventions Among Adults

Eleven reviews served as primary reviews examining the effects of behavioral interventions for smoking cessation among the general adult population (Table 1) (21, 22, 31, 37, 55, 58, 60, 61, 67, 71, 78).

Health and Cessation Outcomes

Data on health outcomes after behavioral interventions were limited to 1 study (79) that was reported in 1 review (58) (Table 2). This study reported no statistically significant differences in rates of total mortality, coronary disease mortality, and lung cancer incidence and mortality at 20-year follow-up among men at high risk for cardiorespiratory disease (n = 1445) (80). However, at 33-year follow-up, there were significantly fewer

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

Study, Year (Reference), by Intervention Type	Quality Rating	Specific Intervention or Population	Last Search Date	Included Studies, *n*	Health Outcomes	Cessation	Harms
Adults: behavioral interventions (26 systematic reviews; 11 primary reviews)							
Behavioral support and counseling							
Stead et al, 2013 (58)*	Good	Physician advice	January 2013	42	√	√	
Rice and Stead, 2013 (55)*	Good	Nursing interventions	June 2013	49		√	
Carr et al, 2012 (26)	Good	Interventions in dental settings	November 2011	14		√	
Cahill et al, 2010 (25)	Good	Stage-based interventions	August 2010	41		√	
Hettema and Hendricks, 2010 (38)†	Fair	Motivational interviewing	June 2008	23		√	
Lai et al, 2010 (43)	Good	Motivational interviewing	April 2009	14		√	
Bodner and Dean, 2009 (23)	Fair	Health professional advice	NR	30		√	
Mottillo et al, 2009 (50)	Fair	Counseling	August 2007	50		√	
Behavioral support as an adjunct to pharmacotherapy							
Stead and Lancaster, 2012 (61)*	Good	Behavioral support as an adjunct to pharmacotherapy	July 2012	38		√	
Print-based self-help materials							
Hartmann-Boyce et al, 2014 (37)*	Good	Print-based self-help materials	April 2014	74		√	
Telephone counseling							
Stead et al, 2013 (60)*	Good	Telephone counseling	May 2013	77		√	
Tzelepis et al, 2011 (66)	Fair	Proactive telephone counseling	December 2008	24		√	
Mobile telephone–based interventions							
Whittaker et al, 2012 (71)*	Fair	Mobile telephone	May 2012	5		√	
Computer-based interventions							
Civljak et al, 2013 (31)*	Good	Internet-based	April 2013	28		√	
Brown, 2013 (24)	Fair	Internet-based, young adults	February 2011	8		√	
Chen et al, 2012 (29)	Good	Computer and electronic aids	December 2009	60		√	
Hutton et al, 2011 (41)	Good	Internet-based	December 2009	21		√	
Myung et al, 2009 (51)	Good	Internet- or computer-based	August 2008	22		√	
Shahab and McEwen, 2009 (56)	Fair	Internet-based	December 2008	11		√	
Biomedical risk assessment							
Bize et al, 2012 (22)*	Good	Biomedical risk assessment	June 2012	15		√	
Exercise							
Ussher et al, 2014 (67)*	Fair	Exercise	May 2014	20		√	
Complementary and alternative therapies							
White et al, 2014 (70)*	Good	Acupuncture	October 2013	38		√	
Di et al, 2014 (33)	Good	Acupuncture	January 2013	25		√	√
Cheng et al, 2012 (30)	Fair	Acupoint stimulation	March 2011	20		√	
Tahiri et al, 2012 (63)	Fair	Alternative therapies	December 2010	14		√	
Barnes et al, 2010 (21)*	Good	Hypnotherapy	July 2010	11		√	√
Adults: pharmacotherapy interventions (9 systematic reviews; 6 primary reviews)							
NRT							
Stead et al, 2012 (59)*	Good	NRT	July 2012	150		√	
Varenicline							
Cahill et al, 2012 (73)*	Good	Varenicline (nicotine receptor partial agonists)	December 2011	20		√	√
Huang et al, 2012 (39)	Good	Varenicline	March 2011	10		√	√
Bupropion SR							
Hughes et al, 2014 (40)*	Good	Bupropion SR (antidepressants)	July 2013	66		√	√
All pharmacotherapy							
Mills et al, 2012 (48)	Fair	NRT, bupropion SR, varenicline	January 2012	146		√	
Tran et al, 2010 (64)	Fair	NRT, bupropion SR, varenicline	February 2009	143		√	√
All pharmacotherapy harms							
Mills et al, 2014 (49)*	Fair	NRT, bupropion SR, varenicline harms	March 2013	63			√
Varenicline harms							
Prochaska and Hilton, 2012 (54)*	Good	Varenicline harms	September 2011	22			√

Continued on following page

Table 1–Continued

Study, Year (Reference), by Intervention Type	Quality Rating	Specific Intervention or Population	Last Search Date	Included Studies, *n*	Health Outcomes	Cessation	Harms
NRT harms							
Mills et al, 2010 (47)*	Fair	NRT harms	November 2009	92			√
Adults: combined pharmacotherapy and behavioral interventions (1 systematic review; 1 primary review)							
Stead and Lancaster, 2012 (57)*	Good	Combined pharmacotherapy and behavioral support	July 2012	41		√	
Adults: electronic nicotine delivery systems (2 RCTs)‡							
Bullen et al, 2013 (74)	Fair	Electronic cigarettes	NA	NA		√	√
Caponnetto et al, 2013 (75)	Fair	Electronic cigarettes	NA	NA		√	√
Pregnant women: behavioral interventions (6 systematic reviews; 1 primary review)							
Chamberlain et al, 2013 (28)*	Good	Behavioral interventions among pregnant women	March 2013	86	√	√	√
Filion et al, 2011 (35)	Fair	Behavioral interventions among pregnant women	June 2010	8		√	
Hettema and Hendricks, 2010 (38)†	Fair	Behavioral interventions among pregnant women	June 2008	8		√	
Likis et al, 2014 (44)	Good	Pharmacotherapy and behavioral interventions among pregnant women	January 2013	59	√	√	√
Su and Buttenheim, 2013 (62)	Fair	Pharmacotherapy and behavioral interventions among pregnant women	December 2012	32		√	
Bondurant and Wedge, 2009 (76)	Good	Pharmacotherapy and behavioral interventions among pregnant women	June 2008	72	√	√	√
Pregnant women: pharmacotherapy interventions (6 systematic reviews; 1 primary review)							
Coleman et al, 2012 (32)*	Good	Pharmacotherapy among pregnant women	March 2012	7§	√	√	√
Myung et al, 2012 (52)	Good	Pharmacotherapy among pregnant women	June 2011	7	√	√	√
Likis et al, 2014 (44)	Good	Pharmacotherapy and behavioral interventions among pregnant women	January 2013	59	√	√	√
Su and Buttenheim, 2013 (62)	Fair	Pharmacotherapy and behavioral interventions among pregnant women	December 2012	32		√	
Bondurant and Wedge, 2009 (76)	Good	Pharmacotherapy and behavioral interventions among pregnant women	June 2008	72	√	√	√

NA = not applicable; NR = not reported; NRT = nicotine replacement therapy; RCT = randomized, controlled trial; SR = sustained release.
* Primary review that served as the basis for the main findings.
† Includes adults and pregnant women and is listed twice in this table.
‡ Not based on a review of reviews; we included 2 RCTs based on a primary search for evidence.
§ We conducted a search for primary evidence to extend this review and added 1 fair-quality trial (77).

deaths from respiratory illnesses among participants who received an intervention than control participants (58).

Several behavioral interventions increased smoking cessation at 6 months or more, including physician- (58) and nurse-delivered (55) counseling interventions, tailored self-help print materials (37), and telephone counseling (60), when compared with minimal intervention or usual care (Table 2 and Appendix Table 2, available at www.annals.org). Smokers who were offered cessation advice by a physician, for example, were 76% more likely to have quit at 6 months or more than those who received no advice or usual care (risk ratio [RR], 1.76 [95% CI, 1.58 to 1.96]; $I^2 = 40\%$; 28 trials; $n = 22\,239$) (58). Both minimal and intensive advice (>20 minutes, additional materials beyond a brochure, or >1 follow-up visit) showed statistically significant increases in cessation rates when compared with control participants who did not receive advice. Direct comparisons between intensive and minimal advice in 15 trials

Table 2. Summary of Evidence for the General Adult Population

Intervention	Included Reviews, *n*	Summary of Findings	Consistency	Major Limitations	Applicability
Health outcomes					
Behavioral	1	1 trial found favorable effects on all-cause and coronary disease mortality and lung cancer incidence and mortality 20 y after an intensive behavioral intervention, although results were not statistically significant.	NA	Only 1 review reported the results of 1 intervention among men on health outcomes. Within that trial, the smoking rate among control participants declined steadily over the follow-up period, narrowing the intervention effect.	1 trial conducted among male civil servants aged 40–59 y in the United Kingdom with high risk for cardio-respiratory disease. Intervention took place in the 1970s.
Pharmacotherapy	0	NA	NA	NA	NA
Combined pharmacotherapy and behavioral	0	NA	NA	NA	NA
ENDS	0 RCTs	NA	NA	NA	NA
Cessation outcomes					
Behavioral	26	Health provider advice and counseling, tailored self-help materials, and telephone counseling showed modest but significant increased smoking cessation at ≥6 mo relative to control participants (18%–96%). Providing more intense adjunctive behavioral support to smokers receiving pharmacotherapy may increase cessation by 9%–24%. Evidence on the use of mobile phone support, Internet-based interventions, and complementary and alternative therapies was limited and not definitive.	Consistent	Individual trials may be represented in >1 review or meta-analysis. Several of the meta-analyses treated comparisons among different trial groups as separate studies and were not consistent in their reporting or handling of multiple comparisons. Fixed-effects models were used in nearly all meta-analyses.	Most of the included studies within each review were done in North America and should be applicable to the U.S. health system. Treatment effects seem to be similar in a range of populations, settings, and types of interventions and in smokers with and without other comorbid conditions. 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.
Pharmacotherapy	6	NRT, bupropion SR, and varenicline improve the chances of smoking cessation. Reviews suggested that NRT might increase smoking abstinence at ≥6 mo by 53%–68%, bupropion SR by 49%–76%, and varenicline by 102%–155%. Absolute cessation differences averaged 7% for NRT, 8.2% for bupropion SR, and 26% for varenicline. There were no significant differences among different NRT products, and relative rates of abstinence were similar across settings. Use of a combination of NRT products increases cessation rates more than the use of a single NRT product. In general, there were no significant differences among different classes of medications in direct comparisons.	Consistent	Possibility of publication bias but unlikely that the presence of additional studies with lower relative risks would alter the findings because of the large number of studies and consistency in findings. Trials with pharmaceutical funding have been shown to have slightly higher effect sizes than nonindustry-funded studies; because of the number of included trials funded by pharma-ceutical companies (particularly for varenicline), the magnitude of the effects may be smaller than estimates suggest.	Most of the included studies within each review were done in North America and should be applicable to the U.S. health system. Treatment effects seem to be similar in a range of populations, settings, and types of interventions and in smokers with and without other comorbid conditions. 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.

Continued on following page

Table 2–Continued

Intervention	Included Reviews, *n*	Summary of Findings	Consistency	Major Limitations	Applicability
Combined pharmacotherapy and behavioral	1	Combined pharmacotherapy and behavioral interventions increase cessation rates by 70%–100% compared with no or minimal treatment.	Consistent	May be risk of bias due to lack of blinding of participants.	Most of the included studies within each review were done in North America and should be applicable to the U.S. health system. Treatment effects seem to be similar in a range of populations, settings, and types of interventions and in smokers with and without other comorbid conditions. 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.
ENDS	2 RCTs	1 trial found no statistically significant difference in biochemically verified abstinence at 6 mo between those receiving electronic cigarettes vs. nicotine patch or placebo electronic cigarettes (n = 657). The other trial (n = 300) found a borderline significant higher cessation rate among those receiving nicotine-containing electronic cigarettes (11%) vs. electronic cigarettes without nicotine cartridges (4%) at 12 mo.	Consistent	Insufficient statistical power to detect differences and differential high loss to follow-up in both trials (22%–40%).	2 trials took place in New Zealand and Italy. Both trials used older models of electronic cigarettes, 1 of which is no longer available. 1 trial was conducted among smokers who did not want to quit.
AEs					
Behavioral	2	Minor AEs related to ear acupuncture, ear acupressure, and other auriculotherapy have been reported. AEs related to other behavioral or complementary and alternative therapies have not been documented.	NA	Only 2 reviews assessed AEs related to behavioral interventions; 1 found no studies that reported AEs.	Limited evidence on harms limits applicability.
Pharmacotherapy	8	NRT, bupropion SR, and varenicline are not associated with an increased risk for major CV AEs. NRT is associated with a higher rate of any CV AE largely driven by low-risk events, typically tachycardia. There was a marginal, nonsignificant increase in serious AEs in participants receiving bupropion SR but no difference for serious psychiatric AEs. The evidence for the safety of varenicline is still under investigation; 1 review suggested a 36% increased risk for nonfatal serious AEs among those receiving varenicline vs. a control intervention.	Consistent	Many trials that report cessation effectiveness do not report AEs, particularly CV- or neuropsychiatric-specific AEs. AEs are typically measured through passive reporting and are therefore susceptible to underreporting.	Likely applicable across settings and populations.

Continued on following page

Table 2–Continued

Intervention	Included Reviews, *n*	Summary of Findings	Consistency	Major Limitations	Applicability
Combined pharmacotherapy and behavioral	0	NA	NA	NA	NA
ENDS	2 RCTs	2 RCTs reported no serious AEs in the intervention or control groups related to product use and no difference in the frequency of AEs among study groups. 1 trial found a higher proportion of serious AEs among the electronic cigarette group vs. the NRT patch group (19.7% vs. 11.8%).	Consistent	Insufficient statistical power to detect differences and differential high loss to follow-up in both trials (22%–40%). 1 study did not report methods for AEs reporting.	2 trials took place in New Zealand and Italy. Both trials used older models of electronic cigarettes, 1 of which is no longer available.

AE = adverse event; CV = cardiovascular; ENDS = electronic nicotine delivery system; NA = not applicable; NRT = nicotine replacement therapy; RCT = randomized, controlled trial; SR = sustained release.

suggested that more intensive advice offered a significant advantage (RR, 1.37 [CI, 1.20 to 1.56]; I^2 = 32%; 15 trials; n = 9775) (58).

A separate meta-analysis of 38 randomized, controlled trials (RCTs) done among more than 15 000 smokers found a small relative benefit of adjunctive behavioral support to pharmacotherapy when compared with pharmacotherapy alone (RR, 1.16 [CI, 1.09 to 1.24]) (61). Cessation rates were relatively high in both the intervention (21.4%) and control (18.3%) groups because both groups received pharmacotherapy (Appendix Table 2).

There was mixed evidence of improved tobacco cessation for the following interventions: nontailored self-help materials (37), interactive or tailored Internet or computer programs (31), mobile telephones (71), biomedical risk assessment (22), exercise (67), acupuncture (70), and hypnotherapy (21) (Appendix Table 2).

Adverse Events

One review reported minor adverse events related to ear acupuncture, ear acupressure, and other auriculotherapy (33). No other reviews found or reported adverse events related to other behavioral or complementary and alternative therapies (Table 2).

Pharmacotherapy Interventions Among Adults

Six reviews served as primary reviews on the effectiveness or harms of NRT, bupropion, or varenicline among current adult tobacco users (Table 1) (40, 47, 49, 54, 59, 73).

Health and Cessation Outcomes

None of the reviews reported the effects of medications for smoking cessation on mortality, morbidity, or other health outcomes. For cessation outcomes, NRT, bupropion, and varenicline all improved rates of smoking cessation in adults at 6-month follow-up or longer (Table 2). Nicotine replacement therapy was effective in all forms and increased relative cessation rates by 53% to 68% when compared with placebo or no NRT (RR, 1.60 [CI, 1.53 to 1.68]; 117 trials; I^2 = 30%; n = 51 265) (Appendix Table 2) (59). No differences were found among NRT products (such as patch, gum, and lozenge) (59). Combining 2 types of NRT was found to be superior to a single form in 9 direct comparisons (RR, 1.34 [CI, 1.18 to 1.51]; 9 trials; I^2 = 34%; n = 4664) (59). A pooled analysis of 44 trials, including 13 728 smokers, found that bupropion increased relative cessation rates by roughly 62% at 6 to 12 months (RR, 1.62 [CI, 1.49 to 1.76]) (40). A smaller body of evidence (14 trials; n = 6166) compared varenicline with placebo and found relatively larger effects on smoking cessation (RR, 2.27 [CI, 2.02 to 2.55]), which was stringently defined as biochemically verified continuous abstinence (73) (Appendix Table 2).

Adverse Events

Pooled results suggested no serious harms from NRT (47, 49) or bupropion (40, 49). Nicotine replacement therapy was associated with an increased risk for any cardiovascular event, driven predominantly by minor cardiovascular events, such as tachycardia and arrhythmia (49). Although 2 reviews found no evidence of an increased risk for any or major cardiovascular adverse events for varenicline (49, 54), a separate meta-analysis of 17 trials found an increased risk for 1 or more serious adverse events among participants who received it (RR, 1.36 [CI, 1.03 to 1.81]; I^2 = 0%; 17 trials; n = 7725) (73).

Combined Behavioral and Pharmacotherapy Interventions Among Adults

A meta-analysis of 40 trials found a statistically significant benefit of combined pharmacotherapy (primarily NRT or bupropion) and behavioral interventions on smoking cessation at 6 months or more when compared with controls (RR, 1.82 [CI, 1.66 to 2.00]; I^2 = 40%; n = 15 021) (57) (Table 2 and Appendix Table 2).

Electronic Nicotine Delivery Systems

On the basis of our search for primary evidence and a review of 25 full-text articles published through 1 March 2015, we identified 2 RCTs that evaluated the effectiveness of ENDS (specifically electronic cigarettes [e-cigarettes]) to help current conventional smokers stop or reduce smoking (Table 2 and Appendix Table 3, available at www.annals.org). In the largest trial, which we rated as fair quality, Bullen and colleagues (74) randomly assigned 657 smokers interested in quitting to a 16-mg nicotine e-cigarette, a 21-mg nicotine patch, or a placebo e-cigarette. All participants were also offered telephone-based support via a smoking quit line. At 6 months, this trial reported no statistically significant differences in biochemically verified continuous smoking abstinence between groups. Smoking cessation was generally low in all 3 groups: 7.3% of participants who received e-cigarettes, 5.8% of those who received nicotine patches, and 4.1% of those who received placebo e-cigarettes. Although more serious adverse events occurred in the nicotine e-cigarette group (27 events [19.7%]) than in the patch group (14 events [11.8%]), the difference was not significant.

Another fair-quality RCT done in Italy by Caponnetto and colleagues (75) randomly assigned 300 conventional smokers who did not intend to quit smoking to 1 of the 3 following regimens using e-cigarette nicotine cartridges: 7.2 mg for 12 weeks, 7.2 mg for 6 weeks followed by 5.4 mg for 6 weeks, or cartridges with no nicotine. Cartridge appearance was identical, but it is unclear whether allocation was concealed. At 52 weeks, biochemically verified cessation rates were borderline significantly different ($P = 0.04$) between participants in both nicotine groups (11%) and those who received the placebo cartridges (4%). The trial did not report comparisons between the individual treatment groups and placebo and reported no difference in the frequency of adverse events among study groups at 12 and 52 weeks. There was substantial loss to follow-up: 36% of participants who received one of the nicotine-containing cartridges and 45% of those who received nonnicotine cartridges did not provide 12-month follow-up data (75).

Behavioral Interventions Among Pregnant Women

Health Outcomes

A meta-analysis of 19 trials found modestly higher mean birthweight among infants born to women who received a behavioral intervention for smoking cessation than those in the control group (40.78 g [CI, 18.45 to 63.10 g]; $I^2 = 0\%$) (28) (Table 3 and Appendix Table 4, available at www.annals.org). Evidence of beneficial health outcomes were also seen in the pooled analyses across all interventions and comparators for preterm birth and low birthweight, with an 18% risk reduction for preterm birth before 37 weeks (RR, 0.82 [CI, 0.70 to 0.96]; $I^2 = 0\%$; 14 trials) and a similar significant estimate for low birthweight (28).

Cessation Outcomes

For smoking cessation, pooled analyses of all behavioral interventions among pregnant women (70 trials) indicated a significant effect during late pregnancy (RR, 1.45 [CI, 1.27 to 1.64]) and moderate to substantial heterogeneity of estimated effects ($I^2 = 60\%$) (Table 3 and Appendix Table 5, available at www.annals.org).

Adverse Events

None of the reviews on behavioral interventions among pregnant women reported adverse events related to the interventions.

Pharmacotherapy Interventions Among Pregnant Women

We included 1 additional fair-quality placebo-controlled trial of NRT (77) on the basis of our search and evaluation of primary evidence. Adding this trial to the review by Coleman and colleagues (32) left 7 trials that evaluated the effects of NRT among pregnant women (Table 3). No trials of bupropion or varenicline among pregnant women met our inclusion criteria.

Health Outcomes

Four NRT placebo-controlled trials reported on preterm birth (delivery at <37 weeks' gestation) (77, 81–83) (Table 3). All but the most recent study estimated effects in the direction of a reduced risk for preterm birth with NRT, including the smallest trial, which had a statistically significant result (RR, 0.41 [CI, 0.18 to 0.94]) (82). These 4 trials also reported birthweight outcomes, 2 of which found significantly higher birthweights among women allocated to the NRT group (82, 83). However, the largest trials (77, 81) did not find a birthweight benefit.

Cessation Outcomes

Meta-analysis of the 5 placebo-controlled efficacy trials among pregnant women ($n = 1922$) showed a nonsignificant pooled effect of NRT on biochemically validated smoking cessation (RR, 1.24 [CI, 0.95 to 1.64]) with low heterogeneity ($I^2 = 0\%$) (Appendix Table 5). Adding the 2 other non–placebo-controlled trials to this analysis increased the estimate of the pooled effect but did not alter the statistical nonsignificance.

Adverse Events

We found no evidence of perinatal harms related to NRT use among pregnant women, but data for assessing rare harms were limited (Table 3). Although the largest trial ($n = 1050$) (81) reported a higher rate of cesarean sections in the NRT group (20% for NRT vs. 15% for placebo; odds ratio, 1.45 [CI, 1.05 to 2.01]), the most recent trial ($n = 402$) did not find a statistical difference (26% vs. 22%, respectively; odds ratio, 1.21 [CI, 0.76 to 1.91]) (77). Miscarriage rates did not differ statistically in the 3 studies included in pooled analyses (RR, 1.24 [CI, 0.37 to 4.17]; $I^2 = 0\%$; $n = 1407$).

Table 3. Summary of Evidence for Pregnant Women

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

Continued on following page

Table 3–Continued

Intervention	Included Reviews, *n*	Summary of Findings	Consistency	Major Limitations	Applicability
AEs					
Behavioral	1	No serious AEs reported.	NA	Inconsistent data collection across trials; most reliant on passive reporting.	Trials mainly conducted in high-income countries, including the United States. Pharmacotherapy trials were placebo-controlled, and outcomes were based on well-established measures used in routine health care settings. Because of the stigma of smoking during pregnancy, it was challenging to recruit pregnant smokers. Those who disclose smoking status and are willing to participate in trials may differ from the general population (e.g., motivation to quit).
Pharmacotherapy	5	No evidence of perinatal harms from NRT. 1 trial found a higher rate of cesarean section for women assigned to NRT; follow-up from the same trial was reassuring for child health outcomes. No trials of bupropion SR or varenicline among pregnant women.	NA	Few trials of NRT, and not all reported consistently on health outcomes and AEs.	

AE = adverse event; NA = not applicable; NRT = nicotine replacement therapy; SR = sustained release.

DISCUSSION

We did this review of reviews to help the USPSTF update its 2009 recommendation on interventions for tobacco cessation among adults. The included reviews represented more than 800 RCTs, many of which were published since the last syntheses done as part of the Public Health Service guideline (which served as the basis for the 2009 USPSTF recommendation) (7, 84). The cumulative evidence suggests that behavioral, pharmacologic, and combined medication and behavioral interventions for smoking cessation that are readily available to primary care patients and clinicians can increase rates of smoking cessation in adults at 6-month follow-up or longer. Behavioral interventions, in particular, effectively help pregnant women stop smoking and improve perinatal health outcomes. Although evidence on the health outcomes of NRT during pregnancy was somewhat reassuring, it offered limited power to rule out rare potential harms.

Our updated findings are generally consistent with the 2008 Public Health Service guideline (7). We found similar evidence of effectiveness among the general adult population for physician advice to quit, varying formats of behavioral interventions (telephone counseling and individual and group counseling), and all 3 first-line medications approved by the U.S. Food and Drug Administration. We also found consistent evidence of effectiveness for behavioral interventions among pregnant women and limited data on the use of medications among pregnant women.

Our findings are also consistent with those of an "overview of reviews" done by Cahill and colleagues (85) on the effectiveness and safety of pharmacotherapies for smoking cessation. Both found that NRT, bupropion, and varenicline were superior to placebo for smoking cessation and that none seemed to have an adverse event risk that would negate their use among the general adult population. Our results also correspond with the results and synthesis of a 2013 review of reviews and recommendations for prevention of smoking during pregnancy by the World Health Organization (86).

Electronic nicotine delivery systems are relatively new technologies, and none of the specific products have been approved as cessation interventions by the U.S. Food and Drug Administration. Regardless, knowledge about these devices may be important for providers who wish to deliver comprehensive smoking-related counseling to their patients. On the basis of our primary review of 2 RCTs, we conclude that available data on the use of ENDS for smoking cessation are quite limited and suggest no benefit among smokers intending to quit. The most recent systematic review on this subject (87) included the same 2 trials that we summarized, and neither suggested a benefit on cessation rates at 6 months or more. In addition, neither of these trials nor the limited number of observational studies included in the recent review reported any serious adverse events considered to be plausibly related to ENDS use. The paucity of trial data on adverse events is

part of the ongoing debate about the appropriateness of their use as a cessation tool.

Our review has several limitations, including our review of reviews approach, the methods and quality of the included reviews that synthesized the bodies of evidence, and the limitations of the primary studies themselves. The comprehensiveness of this review is inevitably limited by the comprehensiveness and quality of the source reviews. Although most of the primary reviews that served as the basis for the main results included evidence through at least 2012, there may be evidence on particular population and intervention subsets that have been published since then. Because of the consistency of the effects within each group over time, we expect that any new trials would have little bearing on the overall results of our synthesis, regardless of sample size or effect estimates.

By adopting a review of reviews approach, we relied on the data as described and assessed by the original reviewers. In doing this, we presumed that each review generally included the full available and eligible evidence base, that data abstraction was accurate, and that analyses were scientifically sound. We were cautious about reporting pooled results for small numbers of studies or highly heterogeneous bodies of evidence. Because the included reviews were not mutually exclusive in their eligibility criteria and, as a result, were not mutually exclusive in their included studies, some individual trials were represented in more than 1 review or meta-analysis. This is particularly true for trials related to behavioral interventions in adults. Although we could not address this overlap by recalculating all of the estimates reported in the reviews because of the effort involved, we do not expect that such adjustments would alter our conclusions. We likely mitigated this potential shortcoming by basing our estimates on primary reviews rather than reporting results from several reviews.

Our syntheses and source reviews identified many areas where more research is warranted. More research is needed on the different types of mobile telephone– and Internet-based behavioral interventions for smoking cessation, including text messaging and smartphone applications, which have high potential applicability to U.S. primary care. Two relatively large trials found favorable effects for personalized text messages (88, 89) and illustrate the particular promise for this new behavioral approach. Direct comparisons among combinations and classes of drugs would be informative (such as use of combinations of NRT and bupropion vs. placebo and NRT or bupropion vs. varenicline). The evidence base for varenicline, although consistent, is smaller than that for NRT and bupropion, and more trials (particularly those that closely monitor harms) would be useful. Further research on the benefit and safety of cessation medications among pregnant women is warranted, including assessment of optimal dosage and treatment timing. A recent pilot RCT on bupropion during pregnancy reported recruitment challenges and suggestions to inform future trials (90). Careful collection of adverse events and systems for deriving long-term consequences of exposure during pregnancy are also needed. Because of the variation and lack of regulatory oversight on the content of ENDS and the limited evidence available from well-designed studies, further research is clearly needed. We identified many current and planned clinical trials on the effectiveness and safety of e-cigarettes as an aid for smoking cessation that are referenced in the full report (14).

The extensive evidence on strategies to help persons stop smoking reviewed in this report confirms the effectiveness of a range of behavioral and pharmacologic interventions when used alone or combined. Clinicians may choose from an array of tools to aid their patients' efforts to quit smoking and can directly provide, refer, or prescribe those that patients find most acceptable, with informed consideration of the probable magnitude of benefits for 6-month cessation and beyond. Implementation of these evidence-based interventions for tobacco control and other comprehensive and systems-level interventions can help to end the burden of preventable disease and premature death.

From Kaiser Permanente Research Affiliates Evidence-based Practice Center, Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon.

Note: This review was done by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality. Agency for Healthcare Research and Quality staff provided oversight for the project and assisted in the external review of the companion draft evidence synthesis.

Acknowledgment: The authors thank the Agency for Healthcare Research and Quality and members of the U.S. Preventive Services Task Force. They also thank the following persons and groups for providing expert or federal partner review of the report: Catherine Chamberlain, MScPHP, MPH, BaSc; Michael Fiore, MD, MPH, MBA; Rashelle Hayes, PhD, MS; Jennifer McClure, PhD; Nancy Rigotti, MD; the Centers for Disease Control and Prevention's National Center for Chronic Disease Prevention and Health Promotion and National Institute for Occupational Safety and Health; and the National Cancer Institute. The authors also thank Smyth Lai, MLS; Kevin Lutz, MFA; and Keshia Bigler at Kaiser Permanente Center for Health Research.

Financial Support: By the Agency for Healthcare Research and Quality (contract HHSA-290-2012-00015-I).

Disclosures: Dr. Patnode reports grants from the Agency for Healthcare Research and Quality (AHRQ) during the conduct of the study. Ms. Henderson reports grants from AHRQ during the conduct of the study. Ms. Thompson reports grants from AHRQ during the conduct of the study. Ms. Senger reports grants from AHRQ during the conduct of the study. Dr. Fortmann reports grants from AHRQ during the conduct of the study. Dr. Whitlock reports grants from AHRQ during the conduct of the study. Authors not listed here have disclosed no conflicts of interest. Forms can be viewed at www.acponline

.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-0171.

Requests for Single Reprints: Reprints are available from the Agency for Healthcare Research and Quality Web site (www.ahrq.gov).

Current author addresses and author contributions are available at www.annals.org.

References

1. **U.S. Department of Health and Human Services.** The Health Consequences of Smoking–50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. Accessed at www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf on 26 August 2015.
2. **Office on Smoking and Health.** How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2010.
3. **Agaku IT, King BA, Dube SR; Centers for Disease Control and Prevention (CDC).** Current cigarette smoking among adults - United States, 2005-2012. MMWR Morb Mortal Wkly Rep. 2014;63:29-34. [PMID: 24430098]
4. **Substance Abuse and Mental Health Services Administration.** Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: U.S. Department of Health and Human Services; 2013. Accessed at http://media.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.pdf on 25 August 2015.
5. **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;150:551-5. [PMID: 19380855]
6. A clinical practice guideline for treating tobacco use and dependence: A U.S. Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA. 2000;283:3244-54. [PMID: 10866874]
7. **Fiore MC, Jaen CR, Baker TB.** Clinical Practice Guideline–Treating Tobacco Use and Dependence: 2008 Update. Rockville, MD: U.S. Department of Health and Human Services; 2008.
8. **Benowitz NL.** Emerging nicotine delivery products. Implications for public health. Ann Am Thorac Soc. 2014;11:231-5. [PMID: 24575992] doi:10.1513/AnnalsATS.201312-433PS
9. **Brody JS.** The promise and problems of e-cigarettes [Editorial]. Am J Respir Crit Care Med. 2014;189:379-80. [PMID: 24528311] doi:10.1164/rccm.201312-2263ED
10. **Bullen C, Knight-West O, O'Brien B, Walker N.** Evidence, not conjecture, should guide clinical practice and policies on e-cigarettes [Letter]. BMJ. 2014;348:g2008. [PMID: 24614753] doi:10.1136/bmj.g2008
11. **Hitchman SC, McNeill A, Brose LS.** Electronic cigarettes: time for an accurate and evidence-based debate [Editorial]. Addiction. 2014;109:867-8. [PMID: 24796396] doi:10.1111/add.12550
12. **Maziak W.** Potential and pitfalls of e-cigarettes [Letter]. JAMA. 2014;311:1922. [PMID: 24825653] doi:10.1001/jama.2014.2995
13. **Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, et al; American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research.** Electronic cigarettes: a policy statement from the American Heart Association. Circulation. 2014;130:1418-36. [PMID: 25156991] doi:10.1161/CIR.0000000000000107
14. **Patnode CP, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP.** Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation in Adults, Including Pregnant Women: A Review of Reviews for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2015. [Forthcoming]
15. **Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al.** Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10. [PMID: 17302989]
16. **Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al.** AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62:1013-20. [PMID: 19230606] doi:10.1016/j.jclinepi.2008.10.009
17. **U.S. Preventive Services Task Force.** Procedure Manual. Rockville, MD: Agency for Healthcare Research and Quality; 2011. Accessed at www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual on 20 August 2015.
18. **Kontopantelis E, Springate DA, Reeves D.** A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. PLoS One. 2013;8:e69930. [PMID: 23922860] doi:10.1371/journal.pone.0069930
19. **Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al.** Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160:267-70. [PMID: 24727843]
20. **Banham L, Gilbody S.** Smoking cessation in severe mental illness: what works? Addiction. 2010;105:1176-89. [PMID: 20491721] doi:10.1111/j.1360-0443.2010.02946.x
21. **Barnes J, Dong CY, McRobbie H, Walker N, Mehta M, Stead LF.** Hypnotherapy for smoking cessation. Cochrane Database Syst Rev. 2010:CD001008. [PMID: 20927723] doi:10.1002/14651858.CD001008.pub2
22. **Bize R, Burnand B, Mueller Y, Rège-Walther M, Camain JY, Cornuz J.** Biomedical risk assessment as an aid for smoking cessation. Cochrane Database Syst Rev. 2012;12:CD004705. [PMID: 23235615] doi:10.1002/14651858.CD004705.pub4
23. **Bodner ME, Dean E.** Advice as a smoking cessation strategy: a systematic review and implications for physical therapists. Physiother Theory Pract. 2009;25:369-407. [PMID: 19842864]
24. **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;10:150-62. [PMID: 23421669] doi:10.1111/wvn.12000
25. **Cahill K, Lancaster T, Green N.** Stage-based interventions for smoking cessation. Cochrane Database Syst Rev. 2010:CD004492. [PMID: 21069681] doi:10.1002/14651858.CD004492.pub4
26. **Carr AB, Ebbert J.** Interventions for tobacco cessation in the dental setting. Cochrane Database Syst Rev. 2012;6:CD005084. [PMID: 22696348] doi:10.1002/14651858.CD005084.pub3
27. **Carson KV, Brinn MP, Peters M, Veale A, Esterman AJ, Smith BJ.** Interventions for smoking cessation in Indigenous populations. Cochrane Database Syst Rev. 2012;1:CD009046. [PMID: 22258998] doi:10.1002/14651858.CD009046.pub2
28. **Chamberlain C, O'Mara-Eves A, Oliver S, Caird JR, Perlen SM, Eades SJ, et al.** Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev. 2013;10:CD001055. [PMID: 24154953] doi:10.1002/14651858.CD001055.pub4
29. **Chen YF, Madan J, Welton N, Yahaya I, Aveyard P, Bauld L, 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;16:1-205, iii-v. [PMID: 23046909] doi:10.3310/hta16380
30. **Cheng HM, Chung YC, Chen HH, Chang YH, Yeh ML.** Systematic review and meta-analysis of the effects of acupoint stimulation on smoking cessation. Am J Chin Med. 2012;40:429-42. [PMID: 22745061]

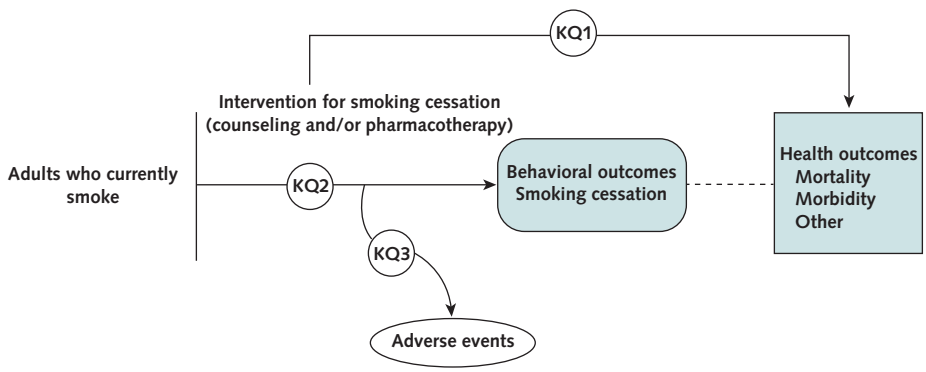
31. **Civljak M, Stead LF, Hartmann-Boyce J, Sheikh A, Car J.** Internet-based interventions for smoking cessation. Cochrane Database Syst Rev. 2013;7:CD007078. [PMID: 23839868] doi:10.1002/14651858.CD007078.pub4
32. **Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J.** Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev. 2012;9:CD010078. [PMID: 22972148] doi:10.1002/14651858.CD010078
33. **Di YM, May BH, Zhang AL, Zhou IW, Worsnop C, Xue CC.** A meta-analysis of ear-acupuncture, ear-acupressure and auriculotherapy for cigarette smoking cessation. Drug Alcohol Depend. 2014;142:14-23. [PMID: 25064021] doi:10.1016/j.drugalcdep.2014.07.002
34. **Ebbert J, Montori VM, Erwin PJ, Stead LF.** Interventions for smokeless tobacco use cessation. Cochrane Database Syst Rev. 2011:CD004306. [PMID: 21328266] doi:10.1002/14651858.CD004306.pub4
35. **Filion KB, Abenhaim HA, Mottillo S, Joseph L, Gervais A, O'Loughlin J, et al.** The effect of smoking cessation counselling in pregnant women: a meta-analysis of randomised controlled trials. BJOG. 2011;118:1422-8. [PMID: 21880109] doi:10.1111/j.1471-0528.2011.03065.x
36. **Gierisch JM, Bastian LA, Calhoun PS, McDuffie JR, Williams JW.** Comparative Effectiveness of Smoking Cessation Treatments for Patients With Depression: A Systematic Review and Meta-analysis of the Evidence. Washington, DC: U.S. Department of Veterans Affairs Evidence-based Synthesis Program; 2010. Accessed at www.hsrd.research.va.gov/publications/esp/smoking-cessation-2010-REPORT.pdf. on 20 August 2015.
37. **Hartmann-Boyce J, Lancaster T, Stead LF.** Print-based self-help interventions for smoking cessation. Cochrane Database Syst Rev. 2014;6:CD001118. [PMID: 24888233] doi:10.1002/14651858.CD001118.pub3
38. **Hettema JE, Hendricks PS.** Motivational interviewing for smoking cessation: a meta-analytic review. J Consult Clin Psychol. 2010;78:868-84. [PMID: 21114344] doi:10.1037/a0021498
39. **Huang Y, Li W, Yang L, Jiang Y, Wu Y.** Long-term efficacy and safety of varenicline for smoking cessation: a systematic review and meta-analysis of randomized controlled trials. J Public Health. 2012;20:355-65.
40. **Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T.** Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2014;1:CD000031. [PMID: 24402784] doi:10.1002/14651858.CD000031.pub4
41. **Hutton HE, Wilson LM, Apelberg BJ, Tang EA, Odelola O, Bass EB, 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;13:227-38. [PMID: 21350042] doi:10.1093/ntr/ntq252
42. **Johnston V, Westphal DW, Glover M, Thomas DP, Segan C, Walker N.** Reducing smoking among indigenous populations: new evidence from a review of trials. Nicotine Tob Res. 2013;15:1329-38. [PMID: 23519776] doi:10.1093/ntr/ntt022
43. **Lai DT, Cahill K, Qin Y, Tang JL.** Motivational interviewing for smoking cessation. Cochrane Database Syst Rev. 2010:CD006936. [PMID: 20091612] doi:10.1002/14651858.CD006936.pub2
44. **Likis FE, Andrews JC, Fonnesbeck CJ, Hartmann KE, Jerome RN, Potter SA, et al.** Smoking Cessation Interventions in Pregnancy and Postpartum Care. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
45. **Liu JJ, Wabnitz C, Davidson E, Bhopal RS, White M, Johnson MR, et al.** Smoking cessation interventions for ethnic minority groups–a systematic review of adapted interventions. Prev Med. 2013;57:765-75. [PMID: 24076130] doi:10.1016/j.ypmed.2013.09.014
46. **Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L.** Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev. 2009:CD001055. [PMID: 19588322] doi:10.1002/14651858.CD001055.pub3
47. **Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO.** Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. Tob Induc Dis. 2010;8:8. [PMID: 20626883] doi:10.1186/1617-9625-8-8
48. **Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO.** Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. Ann Med. 2012;44:588-97. [PMID: 22860882] doi:10.3109/07853890.2012.705016
49. **Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ.** Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation. 2014;129:28-41. [PMID: 24323793] doi:10.1161/CIRCULATIONAHA.113.003961
50. **Mottillo S, Filion KB, Bélisle P, Joseph L, Gervais A, O'Loughlin J, et al.** Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. Eur Heart J. 2009;30:718-30. [PMID: 19109354] doi:10.1093/eurheartj/ehn552
51. **Myung SK, McDonnell DD, Kazinets G, Seo HG, Moskowitz JM.** Effects of Web- and computer-based smoking cessation programs: meta-analysis of randomized controlled trials. Arch Intern Med. 2009;169:929-37. [PMID: 19468084] doi:10.1001/archinternmed.2009.109
52. **Myung SK, Ju W, Jung HS, Park CH, Oh SW, Seo H, et al; Korean Meta-Analysis (KORMA) Study Group.** Efficacy and safety of pharmacotherapy for smoking cessation among pregnant smokers: a meta-analysis. BJOG. 2012;119:1029-39. [PMID: 22780818] doi:10.1111/j.1471-0528.2012.03408.x
53. **Nierkens V, Hartman MA, Nicolaou M, Vissenberg C, Beune EJ, Hosper K, 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:e73373. [PMID: 24116000] doi:10.1371/journal.pone.0073373
54. **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] doi:10.1136/bmj.e2856
55. **Rice VH, Hartmann-Boyce J, Stead LF.** Nursing interventions for smoking cessation. Cochrane Database Syst Rev. 2013;8:CD001188. [PMID: 23939719] doi:10.1002/14651858.CD001188.pub4
56. **Shahab L, McEwen A.** Online support for smoking cessation: a systematic review of the literature. Addiction. 2009;104:1792-804. [PMID: 19832783] doi:10.1111/j.1360-0443.2009.02710.x
57. **Stead LF, Lancaster T.** Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev. 2012;10:CD008286. [PMID: 23076944] doi:10.1002/14651858.CD008286.pub2
58. **Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T.** Physician advice for smoking cessation. Cochrane Database Syst Rev. 2013;5:CD000165. [PMID: 23728631] doi:10.1002/14651858.CD000165.pub4
59. **Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al.** Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2012;11:CD000146. [PMID: 23152200] doi:10.1002/14651858.CD000146.pub4
60. **Stead LF, Hartmann-Boyce J, Perera R, Lancaster T.** Telephone counselling for smoking cessation. Cochrane Database Syst Rev. 2013;8:CD002850. [PMID: 23934971] doi:10.1002/14651858.CD002850.pub3
61. **Stead LF, Lancaster T.** Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2012;12:CD009670. [PMID: 23235680] doi:10.1002/14651858.CD009670.pub2
62. **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;18:714-28. [PMID: 23812798] doi:10.1007/s10995-013-1298-6
63. **Tahiri M, Mottillo S, Joseph L, Pilote L, Eisenberg MJ.** Alternative smoking cessation aids: a meta-analysis of randomized controlled trials. Am J Med. 2012;125:576-84. [PMID: 22502956] doi:10.1016/j.amjmed.2011.09.028

64. **Tran K, Asakawa K, Cimon K, Moulton K, Kaunelis D, Pipe A, et al.** Pharmacologic-based Strategies for Smoking Cessation: Clinical and Cost-Effectiveness Analyses. Ottawa, Ontario, Canada: Canadian Agency for Drugs and Technologies in Health; 2010. Accessed at www.cadth.ca/media/pdf/H0486_Smoking_Cessation_tr_e.pdf on 20 August 2015.
65. **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] doi:10.1002/14651858.CD007253.pub3
66. **Tzelepis F, Paul CL, Walsh RA, McElduff P, Knight J.** Proactive telephone counseling for smoking cessation: meta-analyses by recruitment channel and methodological quality. J Natl Cancer Inst. 2011;103:922-41. [PMID: 21666098] doi:10.1093/jnci/djr169
67. **Ussher MH, Taylor AH, Faulkner GE.** Exercise interventions for smoking cessation. Cochrane Database Syst Rev. 2014;8:CD002295. [PMID: 25170798] doi:10.1002/14651858.CD002295.pub5
68. **van der Meer RM, Willemsen MC, Smit F, Cuijpers P.** Smoking cessation interventions for smokers with current or past depression. Cochrane Database Syst Rev. 2013;8:CD006102. [PMID: 23963776] doi:10.1002/14651858.CD006102.pub2
69. **Villanti AC, McKay HS, Abrams DB, Holtgrave DR, Bowie JV.** Smoking-cessation interventions for U.S. young adults: a systematic review. Am J Prev Med. 2010;39:564-74. [PMID: 21084078] doi:10.1016/j.amepre.2010.08.009
70. **White AR, Rampes H, Liu JP, Stead LF, Campbell J.** Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev. 2014;1:CD000009. [PMID: 24459016] doi:10.1002/14651858.CD000009.pub4
71. **Whittaker R, McRobbie H, Bullen C, Borland R, Rodgers A, Gu Y.** Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev. 2012;11:CD006611. [PMID: 23152238] doi:10.1002/14651858.CD006611.pub3
72. **Zbikowski SM, Magnusson B, Pockey JR, Tindle HA, Weaver KE.** A review of smoking cessation interventions for smokers aged 50 and older. Maturitas. 2012;71:131-41. [PMID: 22209349] doi:10.1016/j.maturitas.2011.11.019
73. **Cahill K, Stead LF, Lancaster T.** Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2012;4:CD006103. [PMID: 22513936] doi:10.1002/14651858.CD006103.pub6
74. **Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al.** Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet. 2013;382:1629-37. [PMID: 24029165] doi:10.1016/S0140-6736(13)61842-5
75. **Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, 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:e66317. [PMID: 23826093] doi:10.1371/journal.pone.0066317
76. **Bondurant S, Wedge R, ed.** Combating Tobacco in Military and Veteran Populations. Washington, DC: National Academies Pr; 2009.
77. **Berlin I, Grangé G, Jacob N, Tanguy ML.** Nicotine patches in pregnant smokers: randomised, placebo controlled, multicentre trial of efficacy. BMJ. 2014;348:g1622. [PMID: 24627552] doi:10.1136/bmj.g1622
78. **White AR, Rampes H, Liu JP, Stead LF, Campbell J.** Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev. 2011:CD000009. [PMID: 21249644] doi:10.1002/14651858.CD000009.pub3
79. **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;32:275-81. [PMID: 370171]
80. **Rose G, Colwell L.** Randomised controlled trial of anti-smoking advice: final (20 year) results. J Epidemiol Community Health. 1992;46:75-7. [PMID: 1573365]
81. **Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, et al; Smoking, Nicotine, and Pregnancy (SNAP) Trial Team.** A randomized trial of nicotine-replacement therapy patches in pregnancy. N Engl J Med. 2012;366:808-18. [PMID: 22375972] doi:10.1056/NEJMoa1109582
82. **Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Feinn R, et al.** Nicotine gum for pregnant smokers: a randomized controlled trial. Obstet Gynecol. 2008;112:859-67. [PMID: 18827129] doi:10.1097/AOG.0b013e318187e1ec
83. **Wisborg K, Henriksen TB, Jespersen LB, Secher NJ.** Nicotine patches for pregnant smokers: a randomized controlled study. Obstet Gynecol. 2000;96:967-71. [PMID: 11084187]
84. **Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff.** A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med. 2008;35:158-76. [PMID: 18617085] doi:10.1016/j.amepre.2008.04.009
85. **Cahill K, Stevens S, Perera R, Lancaster T.** Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;5:CD009329. [PMID: 23728690] doi:10.1002/14651858.CD009329.pub2
86. **World Health Organization.** WHO Recommendations for the Prevention and Management of Tobacco Use and Second-Hand Smoke Exposure in Pregnancy. Geneva: World Health Organization; 2013.
87. **McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P.** Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev. 2014;12:CD010216. [PMID: 25515689] doi:10.1002/14651858.CD010216.pub2
88. **Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin RB, et al.** Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. Tob Control. 2005;14:255-61. [PMID: 16046689]
89. **Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, et al.** Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet. 2011;378:49-55. [PMID: 21722952] doi:10.1016/S0140-6736(11)60701-0
90. **Stotts AL, Northrup TF, Cinciripini PM, Minnix JA, Blalock JA, Mullen PD, et al.** Randomized, controlled pilot trial of bupropion for pregnant smokers: challenges and future directions. Am J Perinatol. 2015;32:351-6. [PMID: 25111040] doi:10.1055/s-0034-1386635

Current Author Addresses: Drs. Patnode, Henderson, Fortmann, and Whitlock; Ms. Thompson; and Ms. Senger: Kaiser Permanente Center for Health Research, 3800 North Interstate Avenue, Portland, OR 97227.

Author Contributions: Conception and design: C.D. Patnode.
Analysis and interpretation of the data: C.D. Patnode, J.T. Henderson, S.P. Fortmann.
Drafting of the article: C.D. Patnode, J.T. Henderson, S.P. Fortmann.
Critical revision of the article for important intellectual content: C.D. Patnode, J.T. Henderson, S.P. Fortmann, E.P. Whitlock.
Final approval of the article: C.D. Patnode, J.T. Henderson, J.H. Thompson, C.A. Senger, S.P. Fortmann, E.P. Whitlock.
Provision of study materials or patients: C.D. Patnode.
Statistical expertise: C.D. Patnode, J.T. Henderson.
Obtaining of funding: E.P. Whitlock.
Administrative, technical, or logistic support: C.D. Patnode, J.H. Thompson, C.A. Senger, E.P. Whitlock.
Collection and assembly of data: C.D. Patnode, J.T. Henderson, J.H. Thompson, C.A. Senger, S.P. Fortmann.

Appendix Figure 1. Analytic framework.

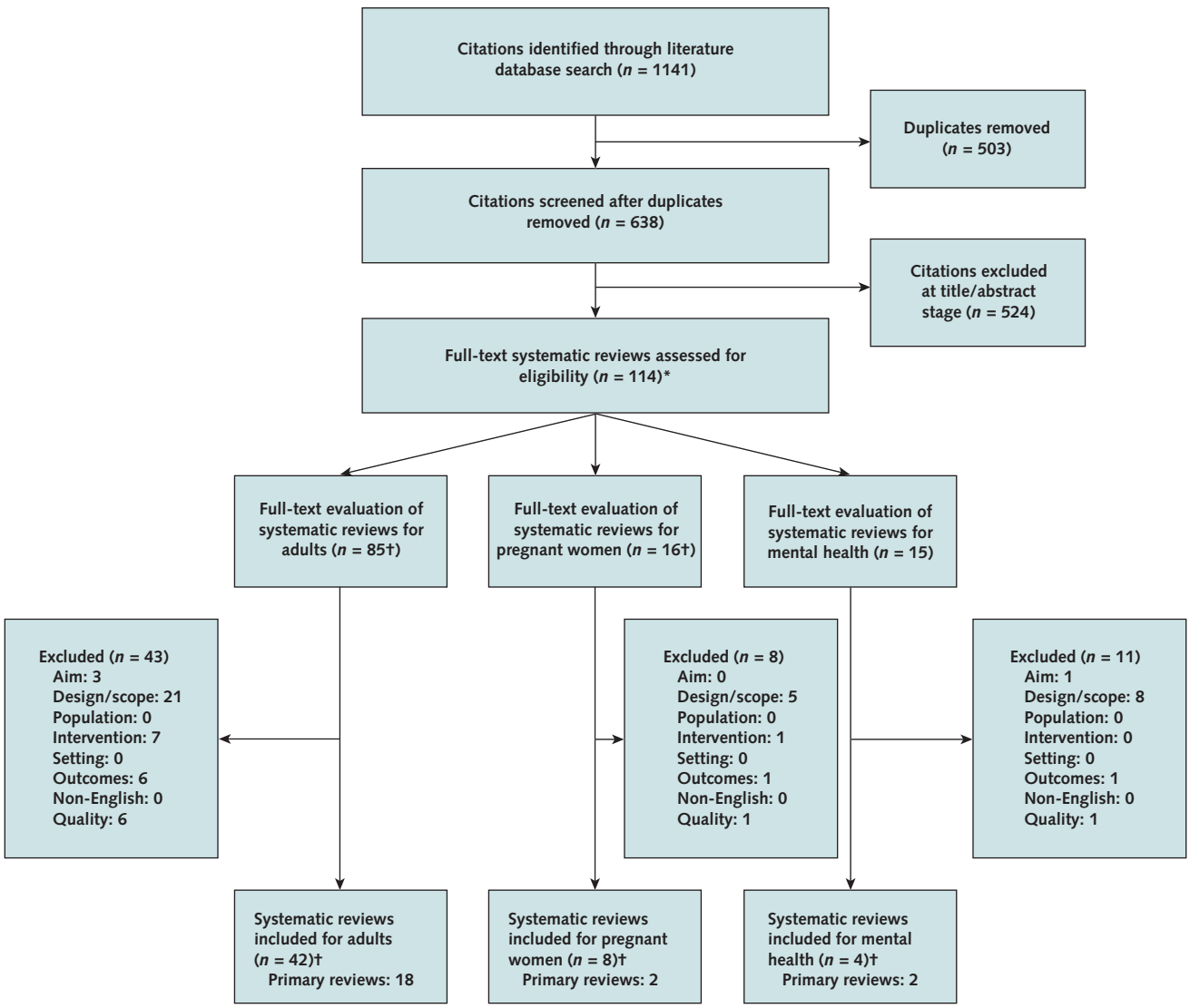


KQ = key question.

Appendix Table 1. Criteria for Choosing the Primary Existing Systematic Reviews

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

Appendix Figure 2. Summary of evidence search and selection.



* 2 studies included both adults and pregnant women.
† Reviews can be counted in multiple intervention areas.

Appendix Table 2. Summary of Smoking Abstinence Results From Reviews of Behavioral Counseling and Pharmacotherapy Interventions for Smoking Cessation Among Adults, by Type of Intervention

Intervention	Control	Studies, *n*	Participants, *n*	Abstinence Measures*	Follow-up, *mo*†	IG Events, *n*	IG Participants, *n*	IG Cessation Rate, %‡	CG Events, *n*	CG Participants, *n*	CG Cessation Rate, %‡	Risk Ratio (95% CI)§	I^2, %
Behavioral interventions for smoking cessation													
Stead et al, 2013 (58)													
Physician advice	No advice/usual care	28	22 239	43% CA 36% BV	≥6	1008	12 583	8.0	462	9656	4.8	1.76 (1.58–1.96)	40
Rice et al, 2013 (55)													
Nursing interventions	Usual care or minimal intervention	35	17 604	29% CA 77% BV	≥6	1273	9589	13.3	906	8015	11.3	1.29 (1.20–1.39)	50
Stead and Lancaster, 2013 (61)													
Behavioral support as an adjunct to pharmacotherapy	Pharmacotherapy (any)	39	15 506	28% CA 79% BV	≥6	1640	7659	21.4	1438	7847	18.3	1.16 (1.09–1.24)	3
Hartmann-Boyce et al, 2014 (37)													
Tailored print-based self-help materials	Control (various)	32	40 890	72% CA 25% BV	≥6	1502	21 017	7.1	1144	19 873	5.8	1.28 (1.18– 1.37)	32
Nontailored print-based self-help materials	Control (various)	33	29 495	42% CA 55% BV	≥6	1080	15 635	6.9	891	13 860	6.4	1.06 (0.98–1.16)	23
Stead et al, 2013 (60)													
Proactive telephone counseling among quit line callers	Control (various)	12	30 182	75% CA 17% BV	≥6	1980	18 428	10.7	895	11 754	7.6	1.41‖ (1.20–1.66)	NR
Proactive telephone counseling (no quit line)	Control (various)	52	30 246	33% CA 35% BV	≥6	2031	15 478	13.1	1433	14 768	9.7	1.27 (1.20–1.36)	42
Whittaker et al, 2012 (71)													
Mobile telephone interventions	Control (various)	5	9100	Pooled results not presented given small number of studies and considerable heterogeneity (I^2 = 79%); results reported narratively.									
Civljak et al, 2013 (31)													
Internet-based interventions	No treatment or other non-Internet-based treatments	23	>45 000	Pooled results not presented given small number of studies in subgroup analyses and considerable statistical heterogeneity; results will be reported narratively.									
Bize et al, 2012 (22)													
Biomedical risk assessment	Control (various)	15	8115	Pooled results not presented given small number of studies in each subgroup and substantial statistical heterogeneity; results reported narratively.									
Ussher et al, 2014 (67)													
Exercise alone or as adjunct to interventions for smoking cessation	Intervention for smoking cessation alone or usual care	20	5870	No meta-analysis conducted due to small number of studies, small sample sizes, and differences in study design and intervention; results reported narratively.									
White et al, 2014 (70)													
Acupuncture	Sham acupuncture	9	1892	33% CA 33% BV	6–12	122	997	12.2	97	895	10.8	1.10 (0.86–1.40)	23
Barnes et al, 2010 (21)													
Hypnotherapy	Brief advice/advice	5	363	Pooled results not presented given small number of studies and clear asymmetry of the results of the included trials, indicating potential publication bias.									
Pharmacotherapy interventions for smoking cessation													
Stead et al, 2012 (59)													
NRT, all forms	Placebo or no NRT¶	117	51 265	57% CA 87% BV	≥6	4704	27 258	17.3	2466	24 007	10.3	1.60 (1.53–1.68)	30
NRT, gum	Placebo or no NRT¶	56	22 581	55% CA 82% BV	≥6	1732	10 596	16.3	1196	11 985	10.0	1.49 (1.40–1.60)	40
NRT, patch	Placebo or no NRT¶	43	19 586	58% CA 88% BV	≥6	1873	11 746	15.9	766	7840	9.8	1.64 (1.52–1.78)	19
NRT, tablets/ lozenges	Placebo or no NRT¶	7	3405	29% CA 100% BV	≥6	337	1808	18.6	134	1597	8.4	1.95 (1.61–2.36)	24
Two forms of NRT (dual)	One form of NRT	9	4664	67% CA 89% BV	≥6	368	1785	20.6	448	2879	15.6	1.34 (1.18–1.51)	34

Continued on following page

Appendix Table 2–Continued

Intervention	Control	Studies, *n*	Participants, *n*	Abstinence Measures*	Follow-up, *mo*†	IG Events, *n*	IG Participants, *n*	IG Cessation Rate, %‡	CG Events, *n*	CG Participants, *n*	CG Cessation Rate, %‡	Risk Ratio (95% CI)§	I^2, %
Hughes et al, 2014 (40)													
Bupropion SR	Placebo or no bupropion SR**	44	13 728	77% CA 95% BV	≥6	1507	7646	19.7	701	6082	11.5	1.62 (1.49–1.76)	18
Bupropion SR	Placebo or no bupropion SR**	17	3862	59% CA 100% BV	6	483	2202	21.9	200	1660	12.0	1.69 (1.45–1.97)	0
Bupropion SR	Placebo or no bupropion SR**	27	9866	81% CA 93% BV	12	1024	5444	18.8	501	4422	11.3	1.59 (1.44–1.76)	39
Cahill et al, 2012 (73)													
Varenicline	Placebo††	14	6166	100% CA 100% BV	≥6	954	3412	28.0	331	2754	12.0	2.27 (2.02–2.55)	63
Combined interventions for smoking cessation													
Stead and Lancaster, 2012 (57)													
Combined pharmacotherapy and behavioral interventions	Control (various)	40	15 021	56% CA 76% BV	≥6	1134	7810	14.5	597	7211	8.3	1.82 (1.66–2.00)	40

BV = biochemically verified; CA = continuous abstinence; CG = control group; IG = intervention group; KQ = key question; NR = not reported; NRT = nicotine replacement therapy; SR = sustained release.

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

† Longest follow-up time point reported.

‡ Weighted average cessation rate.

§ Pooled risk ratios estimated using the Mantel–Haenszel fixed-effects model, unless otherwise noted.

‖ Results from sensitivity analysis using a random-effects model given substantial heterogeneity of fixed-effects model (71%).

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

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

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

Appendix Table 3. Efficacy and Safety of the Use of ENDS for Smoking Cessation

Study	Study Design; Country	Sample Size, *n*	Population	Intervention	Control	Outcomes for Smoking Cessation	Other Outcomes	AEs
Bullen et al, 2013 (74)	RCT; New Zealand	Total: 657 IG: 289 CG1: 295 CG2: 73	Aged ≥18 y, had smoked ≥10 cigarettes per day for at least the past year, wanted to stop smoking	IG: Elusion electronic cigarette (16 mg nicotine) + voluntary quit line behavioral support Duration: From 1 wk before until 12 wk after chosen cessation date	CG1: NRT patch (21-mg nicotine/24 h) CG2: placebo electronic cigarettes + voluntary quit line behavioral support	Continuous abstinence at 6 mo after cessation date (allowing ≤5 cigarettes); biochemically verified: IG: 7.3%* CG1: 5.8% CG2: 4.1%	Median time to relapse: IG: 35 d (95% CI, 15–56)† CG1: 14 d (95% CI, 8–18) CG2: 12 d (95% CI, 5–34) Mean (SE) cigarette consumption at 6 mo among those smoking ≥1 cigarette in past 7 d: IG: 9.7 (0.4) CG1: 7.7 (0.4)‡	No serious events in any groups were related to product use
Caponnetto et al, 2013 (75) Efficiency and Safety of an Electronic Cigarette (ECLAT)	RCT; Italy	Total: 300 IG1: 100 IG2: 100 CG: 100	Aged 18–70 y, had smoked ≥10 cigarettes per day for at least the past 5 y, not currently attempting to quit smoking or wishing to do so in the next 30 d	Categoria 401 Electronic cigarette IG1: 12 wk of 7.2-mg nicotine cartridges used ad libitum IG2: 6 wk of 7.2-mg nicotine cartridges and 6 wk of 5.4-mg nicotine cartridges used ad libitum Baseline visit and 8 follow-up visits (2, 4, 6, 8, 10, 12, 24, 52 wk)	Categoria 401 Electronic cigarette CG: 12 wk of no-nicotine cartridges used ad libitum	Abstinence (not even a puff) since previous study visit; biochemically verified: 24 wk IG1: 12.0%§ IG2: 10.0% CG: 5.0% 52 wk IG1: 13.0%‖ IG2: 9.0% CG: 4.0%	Self-reported number of cigarettes/day: Significant reduction in median value in all 3 groups at each time point; no between-group differences at 12, 24, or 52 wk	No difference in frequency of AEs among study groups at each time point

AE = adverse event; CG = control group; ENDS = electronic nicotine delivery system; IG = intervention group; NR = not reported; NRT = nicotine replacement therapy; RCT = randomized, controlled trial.

* No significant differences between groups. 1- and 3-mo cessation rates also did not differ.

† $P < 0.0001$.

‡ $P = 0.002$.

§ Test for statistical difference not reported.

‖ Significant difference between IG1 and IG2 (11.0%) and CG (4.0%) ($P = 0.04$).

Appendix Table 4. Summary of Perinatal Health Outcome Results of Behavioral Interventions for Smoking Cessation Among Pregnant Women*

Intervention	Control	Studies, *n*	Participants, *n*	Abstinence Measures†	Follow-up‡	IG Events, *n*	IG Participants, *n*	CG Events, *n*	CG Participants, *n*	RR§ or Mean Difference (95% CI)	I^2, %
Outcome: mean birthweight											
All behavioral interventions‖	Usual care or control	19	9859	21% PPA 68% BV	Late pregnancy, including during hospitalization for delivery	NA	4948	NA	4911	40.78 g (18.45–63.10 g)	0
Counseling	Usual care or control	12	5392	17% PPA 67% BV	Late pregnancy, including during hospitalization for delivery	NA	2619	NA	2773	39.93 g (9.12–70.74 g)	0
Outcome: low birthweight (<2500 g)											
All behavioral interventions‖	Usual care or control	14	8562	14% PPA 79% BV	Late pregnancy, including during hospitalization for delivery	304	4298	381	4264	RR: 0.82 (0.71–0.94)	0
Counseling	Usual care or control	8	4339	13% PPA 88% BV	Late pregnancy, including during hospitalization for delivery	151	2090	200	2249	RR: 0.83 (0.68–1.01)	0
Outcome: preterm birth (<37 wk)											
All behavioral interventions‖	Usual care or control	14	7852	29% PPA 79% BV	Late pregnancy, including during hospitalization for delivery	251	3992	307	3860	RR: 0.82 (0.70–0.96)	0
Counseling	Usual care or control	8	3447	25% PPA 89% BV	Late pregnancy, including during hospitalization for delivery	99	1672	117	1775	RR: 0.93 (0.71–1.20)	0
Outcome: stillbirth											
All behavioral interventions‖	Usual care or control	7	5414	0% PPA 57% BV	Late pregnancy, including during hospitalization for delivery	38	2676	31	2738	RR: 1.22 (0.76–1.95)	0
Counseling	Usual care or control	5	2454	0% PPA 80% BV	Late pregnancy, including during hospitalization for delivery	16	1197	14	1257	RR: 1.14 (0.55–2.33)	0

BV = biochemically verified; CG = control group; IG = intervention group; KQ = key question; NA = not applicable; PPA = point prevalence abstinence; RR = risk ratio.
* Data from reference 28.
† Used point prevalence abstinence in late pregnancy for primary outcomes and biochemically validated rates where available.
‡ Longest follow-up time point reported.
§ Pooled RRs estimated using the Mantel–Haenszel random-effects model.
‖ Counseling, health education, feedback, incentives, and social support.

Appendix Table 5. Summary of Smoking Abstinence Results From Reviews of Interventions for Smoking Cessation Among Pregnant Women

Intervention	Control	Studies, *n*	Participants, *n*	Abstinence Measures*	Follow-up†	IG Events, *n*	IG Participants, *n*	IG Cessation Rate, %‡	CG Events, *n*	CG Participants, *n*	CG Cessation Rate, %‡	Risk Ratio (95% CI)§	I^2, %
Chamberlain et al, 2013 (28)													
Any behavioral interventions‖	Usual care or control	70	21 948	0% CA 79% BV	Late pregnancy, including during hospitalization for delivery	1691	11 111	15.2	1213	10 837	11.2	1.45 (1.27–1.64)	60
Counseling	Usual care or control	45	17 681	0% CA 82% BV	Late pregnancy, including during hospitalization for delivery	1283	8830	14.5	992	8851	11.2	1.37 (1.17–1.59)	64
Social support	Usual care or control	10	1683	0% CA 70% BV	Late pregnancy, including during hospitalization for delivery	168	845	19.9	128	838	15.3	1.29 (0.97–1.73)	36
Coleman et al, 2012 (32)													
NRT, all forms¶	Placebo	4	1520	25% CA 100% BV	Late pregnancy, including during hospitalization for delivery	93	762	12.2	71	758	9.4	1.27 (0.95–1.69)	0
Coleman et al, 2012 (32) + Berlin study identified in bridge search (77)													
NRT, all forms**	Placebo	5††	1922	40% CA 100% BV	Late pregnancy, including during hospitalization for delivery	104	965	10.8	81	957	8.5	1.24 (0.95–1.64)	0

BV = biochemically verified; CA = continuous abstinence; CG = control group; IG = intervention group; KQ = key question; NRT = nicotine replacement therapy.
* 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).
† Longest follow-up time point reported.
‡ Weighted average cessation rate.
§ Pooled risk ratios estimated using the Mantel–Haenszel random-effects model.
‖ Counseling, health education, feedback, incentives, and social support.
¶ 3/4 trials used nicotine patches.
** 4/5 trials used nicotine patches.
†† Includes 4 trials identified in the Coleman review and 1 additional trial included from our bridge search.