JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Interventions for Tobacco Cessation in Adults, Including Pregnant Persons

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE It has been estimated that in 2018 nearly 20% of adults in the US were currently using a tobacco product.

OBJECTIVE To systematically review the effectiveness and safety of pharmacotherapy, behavioral interventions, and electronic cigarettes for tobacco cessation among adults, including pregnant persons, to inform the US Preventive Services Task Force.

DATA SOURCES PubMed, PsycInfo, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination of Health Technology Assessment; surveillance through September 25, 2020.

STUDY SELECTION Systematic reviews of tobacco cessation interventions and randomized clinical trials that evaluated the effects of electronic cigarettes (e-cigarettes) or pharmacotherapy among pregnant persons.

DATA EXTRACTION AND SYNTHESIS Independent critical appraisal and data abstraction; qualitative synthesis and random-effects meta-analyses.

MAIN OUTCOMES AND MEASURES Health outcomes, tobacco cessation at 6 months or more, and adverse events.

RESULTS Sixty-seven reviews addressing pharmacotherapy and behavioral interventions were included as well as 9 trials (N = 3942) addressing e-cigarettes for smoking cessation and 7 trials (N = 2285) of nicotine replacement therapy (NRT) use in pregnancy. Combined pharmacotherapy and behavioral interventions (pooled risk ratio [RR], 1.83 [95% CI, 1.68-1.98]), NRT (RR, 1.55 [95% CI, 1.49-1.61]), bupropion (RR, 1.64 [95% CI, 1.52-1.77]), varenicline (RR, 2.24 [95% CI, 2.06-2.43]), and behavioral interventions such as advice from clinicians (RR, 1.76 [95% CI, 1.58-1.96]) were all associated with increased quit rates compared with minimal support or placebo at 6 months or longer. None of the drugs were associated with serious adverse events. Five trials (n = 3117) reported inconsistent findings on the effectiveness of electronic cigarettes on smoking cessation at 6 to 12 months among smokers when compared with placebo or NRT, and none suggested higher rates of serious adverse events. Among pregnant persons, behavioral interventions were associated with greater smoking cessation during late pregnancy (RR, 1.35 [95% CI, 1.23-1.48]), compared with no intervention. Rates of validated cessation among pregnant women allocated to NRT compared with placebo were not significantly different (pooled RR, 1.11 [95% CI, 0.79-1.56], n = 2033).

CONCLUSIONS AND RELEVANCE There is strong evidence that a range of pharmacologic and behavioral interventions, both individually and in combination, are effective in increasing smoking cessation in nonpregnant adults. In pregnancy, behavioral interventions are effective for smoking cessation, but data are limited on the use of pharmacotherapy for smoking cessation. Data on the effectiveness and safety of electronic cigarettes for smoking cessation among adults are also limited and results are inconsistent.

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Supplemental content

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Despite progress in reducing the use of tobacco products by US adults, in 2019 an estimated 20.8% of adults in the US currently used any tobacco product and there are persistent differences in rates of smoking by age, sex, and race/ethnicity.[1] A large range of pharmacologic and behavioral methods are available to help adults quit tobacco use[2]; however in a 2015 survey, among those who tried quitting in the previous year, only 31.2% reported using evidence-based cessation treatments and 7.4% were successful in quitting.[3]

In 2015, the US Preventive Services Task Force (USPSTF) issued 4 recommendations related to tobacco cessation interventions among adults. Two A recommendations were given for behavioral and pharmacotherapy interventions for adults and for behavioral interventions for pregnant women, and 2 I statements were issued: one for pharmacotherapy interventions for pregnant women and one on the use of electronic cigarettes (e-cigarettes) for tobacco cessation among adults and pregnant women.[4] The objective of this review was to inform updated recommendations by the USPSTF.

Methods

Scope of Review

This is an update of a 2015 overview of reviews that supported the 2015 USPSTF recommendation.[5,6] An analytic framework and 3 key questions (KQs) guided the review (**Figure**). Consistent with the 2015 review, an overview of reviews method was primarily used for this update. However, given the insufficient evidence found in 2015, original searches and syntheses of primary evidence were conducted for the benefits and harms of e-cigarettes for smoking cessation and for the benefits and harms of pharmacologic smoking cessation interventions among pregnant women. Details are available in the full report.[8] All main results presented in the full report are also presented in this article; more detailed methods, including review selection and determination of overall credibility and quality of individual reviews and studies, and additional effect estimates for specific types of interventions and comparative effectiveness outcomes, are provided in the full report.

Data Sources and Searches

Three separate literature searches were conducted (eMethods in the Supplement). All searches were restricted to articles in the English language published since January 2014. For reviews, the following databases were searched through April 2019: 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. For primary evidence on e-cigarettes, the CDSR, Cochrane Central Register of Controlled Clinical Trials (CENTRAL), PsycInfo, PubMed, and Scopus were searched through May 2020. For studies of pharmacotherapy tobacco cessation interventions among pregnant women, Medline, CENTRAL, PubMed, and PsycInfo were searched through May 2020. Ongoing surveillance for relevant primary literature and Cochrane systematic reviews was completed through September 25, 2020.

Study Selection

Two researchers independently reviewed all identified abstracts and full-text articles against prespecified eligibility criteria (eTable 1 in the Supplement). Studies were included if they were systematic reviews, with or without meta-analysis, that examined the effectiveness of tobacco cessation interventions for adults. Interventions targeting cessation of any tobacco product, including e-cigarettes, were included and reviews that focused on specific interventions (eg, nicotine replacement therapy [NRT], group counseling) and specific subpopulations (eg, persons with serious mental illness) were eligible. Reviews published by Cochrane and non-Cochrane reviews were included. Narrative (nonsystematic) reviews and other overviews of reviews were excluded. Only the most recent version of updated reviews was included. Separate inclusion criteria were outlined when considering primary evidence related to e-cigarettes and pharmacotherapy interventions among pregnant women (eTable 1 in the Supplement).

Data Extraction and Quality Assessment

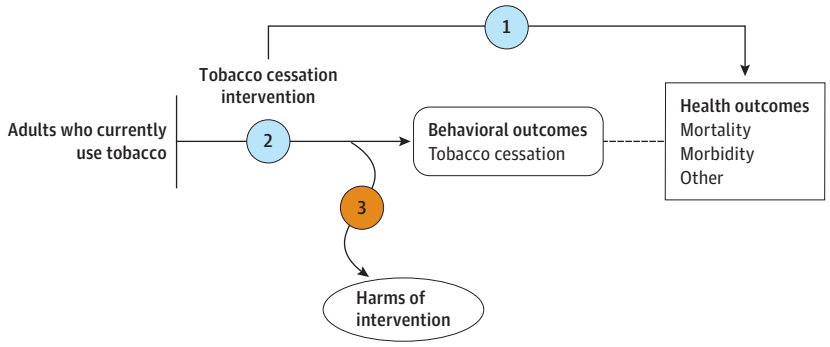
One reviewer completed the AMSTAR-2 (Assessment of Multiple Systematic Reviews 2) tool[9] to rate the credibility of the systematic reviews under consideration for inclusion, and a second reviewer provided an independent assessment using the same tool for all reviews rated critically low. For primary studies, 2 reviewers independently assessed the risk of bias of included evidence using study-design specific criteria. Each review and study were assigned a quality rating of "good," fair," or "poor" according to the USPSTF study design–specific criteria (eTable 2 in the Supplement).[7] Reviews rated as having critically low credibility and primary studies rated as poor quality were excluded. Data from each included review and primary study were abstracted 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 eligibility criteria and the overlapping scope and evidence between many of them, a method was developed to identify 1 or more reviews within each population and intervention group that represented the most current and applicable evidence. These reviews served as the basis for the main findings. All other reviews were examined for complementary or discordant findings. Pooled point estimates presented in the included reviews were reported when appropriate; none of the individual study evidence was reanalyzed. Data from trials of e-cigarette use were not meta-analyzed, given the few number of studies and data reporting. Methods for the meta-analyses of data from trials of pharmacotherapy among pregnant women are described in the full evidence report.

For the overview of reviews method, the strength of the overall body of evidence assigned within the primary systematic review was reported. In most cases, these grades were based on the Grading of Recommendations Assessment, Development and Evaluation 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 the primary evidence syntheses, an overall strength of evidence grade was assigned based on consensus discussions involving at least 2 reviewers.[10]

Figure. Analytic Framework: Interventions for Tobacco Cessation in Adults, Including Pregnant Persons



Key questions

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 are the harms are associated with tobacco cessation interventions in adults, including pregnant women?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a health outcome that immediately follows an intermediate outcome. Additional Information available in the USPSTF Procedure Manual.[7]

Results

This review addressed 2 populations of interest: the general adult population and pregnant women. Within each population, results are organized by KQ.

Evidence for Adults

For the overview of reviews, investigators reviewed 1173 abstracts and 210 full-text articles for possible inclusion for all KQs (eFigure 1 in the Supplement). Sixty-four reviews were identified that met eligibility criteria, including those among an unselected population of adults and those limited to a specific subgroup of adults (**Table 1**).[11-53,57-77] Thirty-two reviews were designated as primary reviews.[11-16,18-20,22,24-30,32-34,38,41,43,45,46,48-53,78] Eleven additional reviews had overlapping evidence with the primary reviews.[17,21,23,31,35,37,39,40,42,44,47] Results of these reviews were consistent with the primary reviews in terms of effect magnitude and statistical significance and are not discussed further. Twenty-one reviews focused on specific subpopulations of adults (eg, people with severe mental illness, smokeless tobacco users).[57-77] These 21 reviews are not discussed here but are included in the full report.[8]

The review of primary evidence on the use of e-cigarettes for smoking cessation resulted in 9 included randomized clinical trials (RCTs) reported in 16 publications; 5 of these RCTs addressed smoking cessation (KQ2) and all addressed potential harms (KQ3) (eFigure 2 in the Supplement).[79-94] None of the e-cigarette trials reported results related to health outcomes (KQ1).

Health Benefits of Interventions

Key Question 1. Do tobacco cessation interventions improve mortality, morbidity, and other health outcomes in adults who currently use tobacco?

One RCT (n = 1445) reported the results of a behavioral tobacco cessation intervention on health outcomes.[95] This study reported no statistically significant differences between intervention and control groups in rates of total mortality (41.5% vs 44.%, *P* = .93), coronary heart disease mortality (17.3% vs 19.9%, *P* = .87), and lung cancer incidence (7.8% vs 8.8%, *P* = .89) at 20-year follow-up among men at high risk for cardiorespiratory disease.[96]

Cessation Benefits of Interventions

Key Question 2. Do tobacco cessation interventions increase tobacco abstinence in adults who currently use tobacco?

Among the general adult population, there was strong evidence from systematic reviews that the combination of pharmacotherapy and behavioral support, all 7 US Food and Drug Administration–approved medications (all forms of NRT, bupropion, varenicline), and a variety of behavioral interventions were statistically significantly associated with an increase in smokers' relative likelihood to quit smoking at 6 or more months as compared with smokers receiving usual care or a minimal stop-smoking intervention (**Table 2**).

The pooled risk ratio (RR) for smoking abstinence at 6 months or more for combined pharmacotherapy plus behavioral support vs usual care or minimal support control groups was 1.83 (95% CI, 1.68-1.98; 52 trials; n = 19 488).[11] Average quit rates in these trials ranged from 2% to 50% (mean, 15.2%) among participants receiving pharmacotherapy and behavioral support vs 0% to 36% (mean, 8.6%) among participants randomized to a control group.

Table 1. Characteristics of Included Systematic Reviews by Review Focus, Intervention, and Last Search Date

Source	Primary review[a]	Quality[b]	Specific intervention or subgroup	Last search date	Total No. of included studies	KQ1 (health outcomes)	KQ2 (cessation)	KQ3 (harms)
Benefits of combined pharmacotherapy and behavioral support (1 review)								
Stead et al,[11] 2016	✓	Moderate	Combined pharmacotherapy and behavioral support	July 2015	53		✓	
Benefits and harms of pharmacotherapy (13 reviews)								
Hartmann-Boyce et al,[12] 2018	✓	High	NRT	July 2017	136		✓	✓
Lindson et al,[13] 2019	✓	High	NRT, different doses, durations, and combinations	April 2018	63		✓	✓
Mills et al,[14] 2010[c]	✓	Moderate	NRT (harms only)	November 2009	120			✓
Howes et al,[15] 2020	✓	High	Bupropion	April 2019	115		✓	✓
Cahill et al,[16] 2016	✓	Moderate	Varenicline	May 2015	44		✓	✓
Agboola et al,[17] 2015		Low	Varenicline	September 2013	19		✓	
Sterling et al,[18] 2016	✓	Low	Varenicline (harms only)	June 2015	38			✓
Thomas et al,[19] 2015	✓	High	Varenicline (harms only)	May 2014	44			✓
Chang et al,[20] 2015	✓	Moderate	Varenicline + NRT	November 2014	3		✓	✓
Windle et al,[21] 2016		Moderate	NRT, bupropion, varenicline	July 2015	123		✓	✓
Mills et al,[22] 2014[c]	✓	Moderate	NRT, bupropion, varenicline (harms only)	March 2013	63			✓
Rosen et al,[23] 2018		Low	NRT, bupropion, varenicline	December 11, July 12, July 13	61		✓	
Hollands et al,[24] 2019	✓	High	Support for medication adherence	September 2018	10		✓	✓
Benefits and harms of behavioral interventions (25 reviews)								
Hartmann-Boyce et al,[25] 2019	✓	High	Behavioral support as an adjunct to pharmacotherapy	June 2018	83		✓	
Stead et al,[26] 2013[c]	✓	High	Physician advice	January 2013	42	✓	✓	
Rice et al,[27] 2017	✓	High	Nurse support	January 2017	59		✓	
Lancaster and Stead,[28] 2017	✓	High	Individual behavioral counseling	May 2016	49		✓	
Stead et al,[29] 2017	✓	Moderate	Group behavioral therapy	May 2016	66		✓	
Lindson et al,[30] 2019	✓	High	Motivational interviewing	August 2018	37		✓	
Denison et al,[31] 2017		Moderate	Cognitive therapy	November 2016	21		✓	
Moyo et al,[32] 2018	✓	Moderate	Decision aids	July 2017	7		✓	
Livingstone-Banks et al,[33] 2019	✓	Moderate	Print-based interventions	March 2018	75		✓	
Matkin et al,[34] 2019	✓	Moderate	Telephone counseling	May 2018	104		✓	
Danielsson et al,[35] 2014		Low	Telephone- or internet-based support	May 2013	74		✓	
Tzelepis et al,[36] 2019	✓	High	Real-time video counseling	August 2019	2		✓	
Palmer et al,[37] 2018		Moderate	Mobile phone-based support	January 2016	18		✓	
Whittaker et al,[38] 2019	✓	High	Mobile phone text messaging and app-based interventions	October 2018	26		✓	

(continued)

Table 1. Characteristics of Included Systematic Reviews by Review Focus, Intervention, and Last Search Date (continued)

Source	Primary review[a]	Quality[b]	Specific intervention or subgroup	Last search date	Total No. of included studies	KQ1 (health outcomes)	KQ2 (cessation)	KQ3 (harms)
Do et al,[39] 2018		Moderate	Mobile phone- and internet-based interventions	March 2017	108		✓	
McCrabb et al,[40] 2019		Moderate	Internet-based interventions	September 2017	45		✓	
Taylor et al,[41] 2017	✓	High	Internet-based interventions	August 2016	77		✓	✓
Graham et al,[42] 2016		Moderate	Internet-based interventions	April 2015	40		✓	
Notley et al,[43] 2019	✓	High	Incentives	July 2018	33		✓	✓
Giles et al,[44] 2014		Moderate	Financial-based incentives	April 2012	8		✓	
Clair et al,[45] 2019	✓	Moderate	Biomedical risk assessment	September 2018	20		✓	
Ussher et al,[46] 2019	✓	High	Exercise	May 2019	24		✓	
Klinsophon et al,[47] 2017		Moderate	Exercise	November 2016	19		✓	
White et al,[48] 2014[c]	✓	High	Acupuncture	October 2013	38		✓	
Barnes et al,[49] 2019	✓	High	Hypnotherapy	July 2018	14		✓	✓
Boyle et al,[50] 2014	✓	High	Electronic health records support	July 2014	16		✓	
Thomas et al,[51] 2017	✓	High	System change interventions	February 2016	7		✓	
Benefits and harms of reduction-to-quit interventions (1 review)								
Lindson et al,[52] 2019[c]	✓	High	Reduce-to-quit interventions	October 2018	51		✓	✓
Benefits and harms of relapse prevention interventions (1 review)								
Livingstone-Banks et al,[53] 2019	✓	Moderate	Relapse prevention	February 2018	77		✓	
Benefits and harms of behavioral interventions in pregnant persons (5 reviews)								
Chamberlain et al,[54] 2017	✓	High	Any behavioral support among pregnant persons	November 2015	102	✓	✓	✓
Griffiths et al,[55] 2018		Moderate	Digital interventions among pregnant persons	May 2017	12		✓	
Livingstone-Banks et al,[53] 2019	✓	Moderate	Relapse prevention among pregnant persons	February 2018	77		✓	
Notley et al,[43] 2019		High	Incentives among pregnant persons	July 2018	10		✓	✓
Wilson et al,[56] 2018		Moderate	Psychotherapy or incentive-based interventions	July 2017	22		✓	
Reviews limited to other subgroups (21 reviews)								
Wu et al,[57] 2015		Moderate	Subgroup: adults not motivated to quit Any tobacco cessation intervention	April 2015	14		✓	✓
Appolonio et al,[58] 2016		High	Subgroup: adults with alcohol or drug dependence Any tobacco cessation intervention	August 2016	34		✓	
Thurgood et al,[59] 2016		High	Subgroup: adults with alcohol or drug dependence Any tobacco cessation intervention	August 2014	17		✓	
Wilson et al,[60] 2017		Moderate	Subgroup: disadvantaged persons Any behavioral support	January 2017	24		✓	

(continued)

Table 1. Characteristics of Included Systematic Reviews by Review Focus, Intervention, and Last Search Date (continued)

Source	Primary review[a]	Quality[b]	Specific intervention or subgroup	Last search date	Total No. of included studies	KQ1 (health outcomes)	KQ2 (cessation)	KQ3 (harms)
Boland et al,[61] 2018		Low	Subgroup: disadvantaged persons Mobile phone– or internet-based support	May 2016	13		✓	
Liu et al,[62] 2013[c]		Low	Subgroup: ethnic minorities Adapted interventions for ethnic minorities	April 2013	28		✓	
Johnston et al,[63] 2013[c]		Low	Subgroup: ethnic minorities Any tobacco cessation intervention	May 2012	5		✓	
Carson et al,[64] 2012[c]		High	Subgroup: ethnic minorities Any tobacco cessation intervention	April 2011	4		✓	✓
Schuit et al,[65] 2017		High	Subgroup: genetic biomarker differences NRT, bupropion, varenicline	August 2016	18		✓	
Khanna et al,[66] 2016		High	Subgroup: persons with SMI Advice	April 2015	0		✓	
Tsoi et al,[67] 2013[c]		High	Subgroup: persons with SMI Any tobacco cessation intervention	October 2012	34		✓	✓
van der Meer et al,[68] 2013[c]		Moderate	Subgroup: persons with SMI Any tobacco cessation intervention	April 2013	49		✓	
Peckham et al,[69] 2017		Moderate	Subgroup: persons with SMI Any tobacco cessation intervention	September 2016	26		✓	✓
Roberts et al,[70] 2016		Moderate	Subgroup: persons with SMI NRT, bupropion, varenicline	December 2014	14		✓	✓
Ahmed et al,[71] 2018		Moderate	Subgroup: persons with SMI Varenicline	July 2018	4		✓	✓
Kishi and Iwata,[72] 2015		Moderate	Subgroup: persons with SMI Varenicline (harms only)	August 2014	7			✓
Wu et al,[73] 2016		High	Subgroup: persons with SMI Varenicline (harms only)	September 2015	8			✓
Smith et al,[74] 2017		Low	Subgroup: sex differences NRT, bupropion, varenicline	December 2015	28		✓	
McKee et al,[75] 2016		High	Subgroup: sex differences Varenicline	December 2014	16		✓	
Ebbert et al,[76] 2015		High	Subgroup: smokeless tobacco users Any tobacco cessation intervention	June 2015	34		✓	✓
Schwartz et al,[77] 2016		Low	Subgroup: smokeless tobacco users Varenicline	February 2014	3		✓	✓

Abbreviations: KQ, key question; NRT, nicotine replacement therapy; SMI, severe mental illness.

[a] Primary reviews are those that represented the most current evidence, most applicable evidence, or both within each population and intervention subgroup and served as the basis for the main findings of this report.

[b] Review credibility assessed using AMSTAR-2 (Assessment of Multiple Systemic Reviews 2).[9]

[c] Included in previous US Preventive Services Task Force review; has not been updated.

Table 2. Smoking Cessation Results at 6 or More Months (KQ2) From Reviews of Tobacco Cessation Interventions Among Adults, by Type of Intervention[a,b]

Source	Intervention	Control	No. of RCTs	No. analyzed	Intervention			Control			Risk ratio (95% CI)	I^2, %
					Events	No.	Quit rate, %[c]	Events	No.	Quit rate, %[c]		
Stead et al,[11] 2016	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 et al,[12] 2018	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 et al,[13] 2019	NRT combination	NRT single form	14	11 356	881	5218	16.9	852	6138	13.9	1.25 (1.15-1.36)	4
Howes et al,[15] 2020	Bupropion	Placebo or no drug	46	17 866	1846	9714	19.0	900	8152	11.0	1.64 (1.52-1.77)	15
Cahill et al,[16] 2016	Varenicline	Placebo	27	12 625	1695	6632	25.6	668	5993	11.1	2.24 (2.06-2.43)	60
Hughes et al,[97] 2014	Nortriptyline	Placebo	6	975	96	480	20.0	49	495	9.9	2.03 (1.48-2.78)	16
Howes et al,[15] 2020	Bupropion	NRT, any form	10	9230	681	3563	19.1	987	4667	21.1	0.99 (0.91-1.09)	18
Howes et al,[15] 2020	Bupropion	Varenicline	6	6286	474	3096	15.3	677	3190	21.2	0.71 (0.64-0.79)	0
Cahill et al,[16] 2016	Varenicline	NRT, any form	8	6264	767	3227	23.8	575	3037	18.9	1.25 (1.14-1.37)	39
Hollands et al,[24] 2019	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 et al,[25] 2019	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 et al,[26] 2013	Physician advice	Usual care	26	22 239	1008	12 583	8.0	462	9656	4.8	1.76 (1.58-1.96)	40
Rice et al,[27] 2017	Nurse advice	Usual care	44	20 881	1607	11 319	14.2	1165	9562	12.2	1.29 (1.21-1.38)	50
Lancaster et al,[28] 2017	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 et al,[29] 2017	Group behavioral intervention	Self-help program	13	4395	249	2388	10.4	116	2007	5.8	1.88 (1.52-2.33)	0
Lindson et al,[30] 2019b	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

(continued)

Table 2. Smoking Cessation Results at 6 or More Months (KQ2) From Reviews of Tobacco Cessation Interventions Among Adults, by Type of Intervention[a,b] (continued)

Source	Intervention	Control	No. of RCTs	No. analyzed	Intervention			Control			Risk ratio (95% CI)	I^2, %
					Events	No.	Quit rate, %[c]	Events	No.	Quit rate, %[c]		
Moyo et al,[32] 2018	Decision aid	Usual care without decision aid	7[d]	1772	NA	NA	NA	NA	NA	NA	NA[e]	NA
Livingstone-Banks et al,[33] 2019b	Print-based, non-tailored self-help materials[f]	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[f]	No self-help	10	14 359	501	6786	7.4	455	7573	6.1	1.34 (1.19-1.51)	0
Matkin et al,[34] 2019	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
Whittaker et al,[38] 2019	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 et al,[36] 2019	Real-time video counselling	Telephone counselling	2	608	30	301	10.0	22	307	7.2	2.15 (0.38-12.04)	66
Taylor et al,[41] 2017	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 et al,[43] 2019	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 et al,[45] 2019	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 et al,[46] 2019	Exercise	No exercise	21	6607	457	3326	13.7	407	3281	12.4	1.08 (0.96-1.22)	0
White et al,[48] 2014	Acupuncture	Sham acupuncture	9	1892	122	997	12.2	97	895	10.8	1.10 (0.86-1.40)	23
Barnes et al,[49] 2019	Hypnotherapy	No intervention or other cessation intervention	14	1926	NA	NA	NA	NA	NA	NA	NA[h]	NA
Boyle et al,[50] 2014	EHR-facilitated interventions	No change to EHR	16[g]	NA[h]	NA	NA	NA	NA	NA	NA	NA[i]	NA
Thomas et al,[51] 2017	System change interventions	No system changes	7	NA[i]	NA	NA	NA	NA	NA	NA	NA[j]	NA

(continued)

Table 2. Smoking Cessation Results at 6 or More Months (KQ2) From Reviews of Tobacco Cessation Interventions Among Adults, by Type of Intervention[a,b] (continued)

Source	Intervention	Control	No. of RCTs	No. analyzed	Intervention			Control			Risk ratio (95% CI)	I^2, %
					Events	No.	Quit rate, %[c]	Events	No.	Quit rate, %[c]		
Lindson et al,[52] 2019c	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

Abbreviations: EHR, electronic health record; NA, not applicable; NRT, nicotine replacement therapy; RCT, randomized clinical trial; RR, risk ratio.

[a] Used strictest available criterion to define abstinence (ie, continuous, sustained, or prolonged abstinence was preferred over point prevalence abstinence, and biochemically validated rates were used when available).

[b] Each review pooled data from the longest follow-up point reported at 6 or more months of follow-up.

[c] Weighted average quit rates.

[d] Includes 3 RCTs and 4 quasi-experimental studies.

[e] No meta-analysis performed. Six studies reported the effects of the intervention on smoking cessation. Only 1 study reported a statistically significant benefit of the use of a decision aid vs usual care on smoking cessation at 6 months.

[f] Irrespective of level of contact and support common to control group.

[g] Includes 7 RCTs and 9 nonrandomized observational studies.

[h] In general, this review found no evidence of a difference in smoking cessation at 6 months' or greater follow-up among trials that compared hypnotherapy vs 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 follow-up between hypnotherapy vs attention-matched smoking cessation behavioral intervention (RR, 1.21 [95% CI, 0.91-1.61]; 6 studies; n = 957; I^2 = 36%).

[i] Only 1 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%, $P < .001$). 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.

[j] 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.

There was also evidence of an association between the use of NRTs, bupropion, and varenicline and smoking abstinence at 6 months or more (Table 2). The pooled RR for abstinence for NRT was 1.55 (95% CI, 1.49-1.61; 133 trials; n = 64 640)[12]; for bupropion, 1.64 (95% CI, 1.52-1.77; 46 trials; n = 17 866)[15]; and for varenicline, 2.24 (95% CI, 2.06-2.43; 27 trials; n = 12 625)[16] when compared with placebo or no drug. In all cases, behavioral support to quit smoking was provided to both intervention and control participants. There was also an association between combined NRT (typically a long- and short-acting therapy) and quitting at 6 months or more (RR, 1.25 [95% CI, 1.15-1.36]; 14 trials; n = 11 356) compared with a single form of NRT.[13] Pooled analysis of trials directly comparing NRT and bupropion did not suggest a difference between the 2 types of pharmacotherapy (RR, 0.99 [95% CI, 0.91-1.09]; 10 trials; n = 8230)[15]; however, varenicline has been shown to be superior to both NRT (RR, 1.25 [95% CI, 1.14-1.37]; 8 trials; n = 6264)[16] and bupropion (RR [bupropion vs varenicline], 0.71 [95% CI, 0.64-0.79]; 6 trials; n = 6286)[15] in achieving abstinence at 6 months or more, although there are fewer trials testing these differences. There is limited evidence for the use of other antidepressants and nicotine receptor partial agonists for their effectiveness in helping people stop smoking.[15,16]

Compared with various controls, behavioral interventions such as in-person advice and support from clinicians[26,27]; individual-,[28] group-,[29] telephone-,[34] and mobile phone–based[38] support; interactive and tailored internet-based interventions[41]; and the use of incentives[43] were associated with increased relative smoking cessation at 6 or more months (15% to 88% range of relative effects). Pooled results for all comparisons are reported in Table 2. For example, smoking cessation advice from a physician or nurse was associated with pooled RRs of 1.76 (95% CI, 1.58-1.96; 28 trials; n = 22 239)[26] and 1.29 (95% CI, 1.21-1.38; 44 trials; n = 20 881),[27] respectively. Behavioral support, when added to pharmacotherapy, was also associated with increased rates of smoking cessation when compared with pharmacotherapy alone (RR, 1.15 [95% CI, 1.08-1.22]; 65 trials; n = 23 331).[25] There was a lack of clear benefit of motivational interviewing[30]; decision aids[32]; real-time video counseling[36]; print-based, nontailored self-help materials[33]; biomedical risk assessment[45]; exercise[46]; acupuncture[48]; hypnotherapy[49]; and systems-level interventions[50,51] compared with controls; however, there was substantially less evidence related to each of these interventions, and many individual trials of these interventions showed positive effects.

There was no evidence to suggest that the benefits and harms of pharmacotherapy and behavioral interventions, alone and combined, differed when offered to specific subpopulations of adults, including those with mental health conditions, ethnic minorities, or smokeless tobacco users. Where pooled results were presented, the direction and magnitude of effects were almost identical to those seen with the broader evidence base, although very few direct comparisons between subgroups were presented. While some reviews found evidence of potential effect modification by specific intervention, population, or study design characteristics, there was no individual factor that consistently predicted greater treatment effects across reviews.

Five trials (n = 3117)[80,81,90,91,93] were included that evaluated the effectiveness of using e-cigarettes to help current conventional smokers stop or reduce smoking compared with placebo or nicotine replacement therapy (eTable 3 in the Supplement). The types of e-cigarettes, nicotine content, delivery of the intervention, and additional intervention components differed across all 5 trials, as did the comparisons (eTable 3 in the Supplement). Mixed findings were reported on the effectiveness of e-cigarettes on smoking cessation at 6 to 12 months among adult smokers when compared with placebo devices or NRT (eTable 4 in the Supplement). In 2 of the 5 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[90] or NRT plus nonnicotine e-cigarettes[91] at 6- to 12-month follow-up. In both trials, continued use of e-cigarettes was high at 6- and 12-month follow-up (approximately 3-9 months after the treatment phase), with 45% to 80% of participants still using nicotine-based e-cigarettes as opposed to approximately 9% to 40% of participants still using NRT. Another trial (n = 300) compared the use of e-cigarettes (2 groups using different nicotine concentrations) with placebo at 12 months and found 11% abstinence in the nicotine-containing e-cigarette groups compared with 4% abstinence in the placebo group (P = .04), but 27% of those who quit smoking continued to use e-cigarettes at 1 year.[81] The remaining 2 trials (n = 807) reported no clear difference in the rates of smoking cessation among those randomized to nicotine e-cigarettes vs placebo e-cigarettes[80] or nicotine gum at 6 to 12 months' follow-up.[93]

Harms of Interventions

Key Question 3. What harms are associated with tobacco cessation interventions in adults?

Nine primary reviews reported adverse events related to pharmacotherapy interventions for smoking cessation in general adult populations.[12-16,18-20,22] There was no association between the use of NRT, bupropion, or varenicline and serious adverse events, including major cardiovascular adverse events or serious neuropsychiatric events, as compared with placebo or nondrug control groups. Few reviews on behavioral interventions captured information on potential harms, and none suggested serious adverse events that arose. Nine trials reported on the potential short-term harms of e-cigarette use for cessation; none suggested relatively higher rates of serious adverse events.[80-84,86,90,91,93]

Evidence for Pregnant Women

Based on a primary literature review of 64 full-text articles, 7 RCTs (n = 2285) (reported in 12 publications)[98-109] that evaluated the use of NRT among pregnant women were included (eTable 5 in the Supplement). Additionally, 5 large observational studies (n = 1 293 379) (reported in 6 publications)[110-115] were included that reported on the harms of NRT, bupropion, or varenicline use (eFigure 3 in the Supplement).

Using the overview of reviews approach, 5 reviews were identified that addressed the benefits and harms of behavioral interventions for supporting women to stop smoking during pregnancy (Table 1).[43,53-56] A 2017 Cochrane review included the most comprehensive evidence synthesis of tobacco cessation behavioral support interventions for pregnant women and was used as the basis for the findings presented here.[54] The other identified reviews were mostly duplicative and the results were entirely consistent with the Cochrane review.

No studies were identified that addressed the benefits or harms of the use of e-cigarettes to help pregnant women quit smoking.

Health Benefits of Interventions

Key Question 1. Do tobacco cessation interventions improve mortality, morbidity, and other health outcomes in pregnant women who currently use tobacco?

All 7 included RCTs (n = 2285) were designed to test the effectiveness of NRT on smoking cessation and reported infant, child, and maternal health.[98,99,102,105-107,109] Five placebo-controlled trials reported on preterm birth (delivery at <37 weeks' gestation).[98,99,105,106,109] The most recent study, conducted in 2017, reported a statistically significant lower incidence of preterm delivery among those in the NRT inhaler group (3/67 [4.5%]) compared with the placebo group (10/67 [14.9%]) (P = .03) after controlling for history of preterm birth.[106] Within the other trials, 1 (n = 403) reported similar numbers of women with preterm birth in the NRT and placebo groups (14.0% vs 13.5%, respectively),[98] 2 (n = 1301) reported only slightly fewer women with preterm birth in the NRT group,[99,109] and the study with the fewest patients (n = 194) reported reduced incidence of preterm birth with NRT compared with placebo (RR, 0.39 [95% CI, 0.17-0.91]).[105] The 3 placebo-controlled trials that did not report statistically significant differences had larger samples and estimated effects closer to null, with RRs ranging from 0.85 to 1.04.[98,99,109] Two trials without placebo controls were imprecise (very wide CIs) and estimated effects in opposite directions.[102,107]

All 7 trials reported the association between NRT and mean birth weight.[98,99,102,105-107,109] Two placebo-controlled trials found significantly higher mean birth weights among women allocated to the NRT group,[105,109] and only one of these trials[105] reported similar effect for the proportion of infants categorized as having low birth weight. The 2 largest, good-quality, placebo-controlled trials of NRT patch interventions (n = 403 and n = 1051) did not find evidence of increased infant birth weight with NRT treatment.[98,99]

One hundred two RCTs were included in a 2017 review that addressed the effects of behavioral smoking cessation interventions during pregnancy on smoking behavior and perinatal health outcomes.[54] Of the 102 included trials, 19 study groups reported rates of preterm birth (<37 weeks' gestation), 26 study groups reported mean birth weight, and 17 groups reported rates of low-birth-weight infants (<2500 g).[54] Other, less commonly reported data included stillbirths (8 trials), perinatal deaths (4 trials), and neonatal deaths (5 trials) (results related to these outcomes are included in the full report).

Of the 19 trials reporting the effects of a behavioral intervention on preterm birth (less than 37 weeks' gestation), results were mixed, although the majority reported a reduced risk of preterm

birth among women within the behavioral interventions vs control groups.[54] The review's meta-analysis of these trials found no significant association with behavioral interventions compared with controls on rates of preterm birth (RR, 0.93 [95% CI 0.77-1.11]; 19 trials; n = 9222) (eTable 6 in the Supplement). When all 26 studies that reported mean birth weight were combined, there was evidence that behavioral smoking cessation interventions were associated with a higher mean birth weight (55.60 g, compared with usual care control interventions; mean difference, 55.60 g [95% CI, 29.82-81.38]; 26 trials; n = 11 338) (eTable 6 in the Supplement).[54] A pooled analysis of 18 RCTs also found a 17% risk reduction for delivery of a low-birth-weight infant (<2500 g) (RR, 0.83 [95% CI, 072-0.94]; 18 trials; n = 9402) (eTable 6 in the Supplement).

Cessation Benefits of Interventions

Key Question 2. Do tobacco cessation interventions increase tobacco abstinence in pregnant women who currently use tobacco?

There was no evidence of differences in rates of smoking cessation among pregnant women randomized to NRT vs placebo or no intervention within the included trials. Meta-analysis of 5 placebo-controlled trials found a pooled RR of 1.11 (95% CI, 0.79-1.56]; n = 2033) for NRT vs placebo (eFigure 4 in the Supplement).[98,99,105,106,109] Quit rates in these trials ranged from 5% to 28% in the intervention groups and 5% to 25% in the control groups (mean, 11.8% vs 10.6%). The results of the 2 smaller trials with no treatment controls[102,107] were not statistically significant, and estimates of efficacy were greater than for the placebo-controlled trials.

Within the Cochrane review on behavioral interventions among pregnant women, of the 120 study groups included in the review, 97 groups reported the primary outcome measure of smoking abstinence in late pregnancy, up to and including the period of hospitalization for birth.[54] Pooled analyses of all behavioral interventions, regardless of type of behavioral support and including self-reported outcomes, indicated a statistically significant association with smoking cessation in late pregnancy when compared with usual care or a minimal intervention (RR, 1.35 [95% CI, 1.23-1.48]; 97 trials; n = 26 637) (eTable 7 in the Supplement). The results were similarly associated with a beneficial effect when restricted to trials comparing counseling with usual care (RR, 1.44 [95% CI, 1.19-1.73]; 30 trials; n = 12 432). There was some evidence that the positive association 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, 1.26-2.01; 11 trials) at 0 to 5 months postpartum, 1.33 (95% CI, 1.00-1.77; 6 trials) at 6 to 11 months postpartum, and 2.20 (95% CI, 1.23-3.96; 2 trials) at 12 to 17 months.[54]

Harms of Interventions

Key Question 3. What harms are associated with tobacco cessation interventions in pregnant women?

There was no evidence of perinatal harms related to NRT use among pregnant women, but data for assessing rare harms were very limited.[98,99,102,105-107,109] Two larger trials reported stillbirths and congenital malformations and reported few events and no differences in the outcome between study groups.[98,99] Trials reporting miscarriage[98,99,106] and neonatal deaths[98,99,105] reported few events and no difference between study groups. One trial provided extended follow-up and did not find differences in longer-term developmental or respiratory harms associated with NRT use during pregnancy.[101] Evidence from 5 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 vs those unexposed to medications but whose mothers smoked.[110-115] Behavioral smoking cessation interventions were found to have minimal adverse effects.[54]

Discussion

This evidence review evaluated interventions for tobacco cessation in adults; the evidence is summarized in **Table 3**. The results are generally consistent with the conclusions of the 2020 Surgeon General's report on smoking cessation.[2] There is moderate- to high-certainty evidence that all 7 US Food and Drug Administration–approved medications for smoking 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 among adults at 6 months and longer compared with usual care or brief self-help materials. 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 since the previous review,[5,6] the effect estimates for each pooled comparison have been remarkably stable for at least the past 3 decades.

Nevertheless, various questions about tobacco cessation interventions have not yet been answered. Evidence is still needed to compare different forms, doses, and durations of drugs; to compare drugs with one another; to evaluate remotely delivered interventions vs minimal support; and to test interventions in special populations for which the effectiveness may differ from that in the general population (eg, pregnant women, persons with current severe mental illness, those with physical disabilities, nondaily and intermittent smokers), including direct subgroup comparisons.

Evidence on the potential benefits and harms of pharmacotherapy for smoking cessation during pregnancy is limited, with few placebo-controlled trials and limited power for detecting both potential benefits and harms (Table 3). In contrast to the findings in this review, a recent Cochrane review concluded that there was low-quality evidence suggesting that NRT may be more effective than placebo and nonplacebo controls.[117] There was unclear evidence of an association when limited to only placebo-controlled trials,[117] however, a finding similar to this review. Careful collection of adverse events information, including long-term consequences of stop-smoking medications, 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.

Table 3. Summary of Evidence

Intervention	No. of included studies and participants[a]	Summary of findings	Consistency and precision	Other limitations	Strength of evidence[b]
KQ1: health outcomes (general adults)					
Combined pharmacotherapy and behavioral	0	NA	NA	NA	Insufficient
Pharmacotherapy	0	NA	NA	NA	Insufficient
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 y after an intensive behavioral intervention, although results were not statistically significant	NA	Only 1 review reported the results of 1 intervention in men; within that trial, the rate of smoking among control group participants declined steadily over the follow-up period, narrowing the intervention effect	Low evidence of potential benefit
Electronic cigarettes	0 RCTs	NA	NA	NA	Insufficient
KQ2: cessation outcomes (general adults)					
Combined pharmacotherpy and behavioral	1 review (53 RCTs, n = 25 375)	Combined pharmacotherapy and behavioral interventions increased smoking quit rates by 68% to 98% compared with no or minimal treatment (RR, 1.83 [95% CI, 1.68-1.98]) at ≥6 mo follow-up	Reasonably consistent; reasonably precise	May be risk of bias due to lack of blinding of participants	High evidence of benefit[c]
Pharmacotherapy	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 mo or longer by 49% to 61% (RR, 1.55 [95% CI, 1.49-1.61]); bupropion by 49% to 76% (RR, 1.62 [95% CI, 1.49-1.76]); and varenicline by 106% to 143% (RR, 2.24 [95% CI, 2.06-2.43]) 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, 1.15-1.36]) Direct comparisons between drugs suggested that varenicline may be superior to NRT and bupropion in achieving smoking abstinence at ≥6 mo[e]	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[d]
Behavioral	20 reviews (830 RCTs, n > 500 000)	Clinician 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 mo or more relative to controls (15%-88%); for example, RR, 1.76 (95% CI, 1.58-1.96) for physician advice vs minimal controls or usual care Providing more intense adjunctive behavioral support to smokers receiving pharmacotherapy may increase cessation by 8% to 22% (RR, 1.15 [95% CI, 1.08-1.22]) 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 1 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[f]

(continued)

Table 3. Summary of Evidence (continued)

Intervention	No. of included studies and participants[a]	Summary of findings	Consistency and precision	Other limitations	Strength of evidence[b]
Relapse prevention	1 review (77 RCTs, n = 67 285)	Analyses of behavioral interventions among abstainers did not detect an effect in studies of both assisted abstainers (RR, 0.99 [95% CI, 0.87-1.13]; I^2 = 56%; 10 studies; n = 5408) and unaided abstainers (RR, 1.06 [95% CI, 0.96-1.16]; I^2 = 1%; 5 studies; 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 2 studies NRT was found to help in unassisted abstainers, but no difference was seen among those who achieved abstinence with NRT None of the 6 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 intervention; moderate evidence of benefit of varenicline; low evidence of no benefit of bupropion or NRT
e-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 nonnicotine e-cigarettes at 6- to 12-mo follow-up, although continued use of e-cigarettes remained high after the treatment phase Another trial (n = 300) found a borderline statistically significant higher quit rate among persons receiving nicotine-containing e-cigarettes (11%) vs nonnicotine e-cigarettes (4%) at 12 mo (P = .04), but 27% of those who quit smoking continued to use e-cigarettes at 1 y The remaining 2 trials found no statistically significant difference in biochemically verified abstinence at 6 mo between those receiving e-cigarettes vs nicotine patch or placebo e-cigarettes (n = 807)	Inconsistent; imprecise	Limited statistical power to detect differences and differential loss to follow-up in all 5 trials (22%-50%) Wide variance of nicotine concentrations in e-cigarette interventions (7.8 mg vs 18 mg)	Insufficient
KQ3: harms (general adults)					
Combined pharmacotherapy and behavioral	0 reviews	NA	NA	NA	Moderate evidence of no harms[g]
Pharmacotherapy	15 reviews	NRT, bupropion, and varenicline were not associated with an increased risk in major cardiovascular or neuropsychiatric adverse events NRT was associated with a higher rate of any cardiovascular 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 those with vs without severe mental illness	Reasonably consistent; reasonably precise	Many trials that report cessation effectiveness do not report adverse events, particularly cardiovascular- or neuropsychiatric-specific adverse events Adverse events typically measured through passive reporting and therefore susceptible to underreporting	Moderate evidence of no serious harms[g]
Behavioral	3 reviews	There was no evidence that behavioral tobacco cessation interventions are associated with serious adverse events	NA	Very few reviews assessed adverse events related to behavioral interventions	Moderate evidence of no harms[g,h]

(continued)

Table 3. Summary of Evidence (continued)

Intervention	No. of included studies and participants[a]	Summary of findings	Consistency and precision	Other limitations	Strength of evidence[b]
Electronic cigarettes	9 RCTs (n = 3942)	No trials reported serious adverse events in either the intervention or the control groups related to product use and no significant differences in the frequency of adverse events among study groups Coughing, nausea, throat irritation and sleep disruption were the most reported adverse effects of e-cigarette use	Reasonably consistent; imprecise	Limited statistical power to detect differences and differential loss to follow-up in all 3 trials (22%-39%) One study did not report methods for reporting adverse events	Insufficient
KQ1: health outcomes (pregnant persons)					
Pharmacotherapy	7 RCTs (n = 2285)	Limited evidence of NRT on perinatal and child health benefits Five placebo-controlled NRT trials reported preterm births with the 3 largest trials reporting effects close to null and 2 reporting reduced risk with NRT These 5 trials also reported birth weight; the 2 largest placebo-controlled trials reported no difference with NRT, and 2 trials reported higher mean birth weights associated with NRT The risk for low birth weight was lower in the smallest trial, and results were mixed but null for the others Follow-up data from the largest NRT trial found higher rate of "survival with no impairment" at 2 y among children of women assigned to NRT intervention vs placebo (73% vs 65%; OR, 1.40 [95% CI 1.05-1.86]) 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 follow-up and measurement of perinatal outcomes	Insufficient evidence for birth outcomes and child health outcomes
Behavioral	1 review (26 RCTs, n = 12 338)	Suggestive benefit of behavioral interventions on mean birth weight (mean difference, 55.60 [95% CI, 29.82-81.38]) and low birth weight (RR, 0.83 [95% CI, 0.72-0.94]), vs usual care or control Uncertain evidence on the effect of behavioral interventions on preterm birth (RR, 0.93 [95% CI, 0.77-1.11]) and stillbirths (RR, 1.20 [95% CI, 0.76-1.90])	Reasonably consistent; reasonably precise		High evidence of potential benefit on mean birth weight and risk of preterm birth
Electronic cigarettes	0	NA	NA	NA	Insufficient
KQ2: cessation outcomes (pregnant persons)					
Pharmacotherapy	7 RCTs (n = 2285)	No statistical evidence of NRT efficacy for validated smoking cessation in late pregnancy (RR, 1.11, 95% CI, 0.79-1.56) in pooled analysis of 5 placebo-controlled trials Limited power and all trials in the direction of benefit, including 2 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 who declined, and low participation rates	Low evidence of no benefit

(continued)

Table 3. Summary of Evidence (continued)

Intervention	No. of included studies and participants[a]	Summary of findings	Consistency and precision	Other limitations	Strength of evidence[b]
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, 1.23-1.48]), with a similar benefit when limited to the most common intervention (counseling) vs usual care (RR, 1.44 [95% CI, 1.19-1.73]) Heterogeneity was moderate for the pooled effect (44%), but there was no definitive evidence of subgroup effects by study, population, or intervention characteristics	Reasonably consistent; reasonably precise	Minimal information on the number of women who were eligible for inclusion or approached to take part in the trials 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 follow-up	Moderate evidence of benefit
Relapse prevention	1 review (18 RCTs, n = 5545)	No clear benefit on relapse prevention at the end of pregnancy (RR, 1.05 [95% CI, 0.99-1.11]; 8 studies; n = 1523; I^2 = 0%) or during the postpartum period (RR, 1.02 [95% CI, 0.94-1.09]; 15 studies; n = 4606; I^2 = 3%)	Inconsistent; imprecise	Variable interventions tested	Low evidence of no benefit of behavioral interventions
e-Cigarettes	0	NA	NA	NA	Insufficient
KQ3: harms (pregnant persons)					
Pharmacotherapy	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 (KQ1) Two-year follow-up from 1 NRT trial did not suggest harms (KQ1) No trials of bupropion or varenicline among pregnant women Observational evidence did not indicate harms of major congenital anomalies, stillbirth, premature birth, or low birth weight associated with NRT, bupropion, or varenicline	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 differences across a range of population characteristics among comparison groups	Low evidence of no harm
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 effects reported an improvement in women's psychological well-being, and none reported negative effects	Reasonably consistent; reasonably precise	Measures of adverse events rarely reported; most reliant on passive reporting	Moderate evidence of no harm
e-Cigarettes	0	NA	NA	NA	Insufficient

Abbreviations: e-cigarette, electronic cigarette; NA, not applicable; NRT, nicotine replacement therapy; OR, odds ratio; RCT, randomized clinical trial; RR, risk ratio.

[a] 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.

[b] For the review-of-reviews method, the strength of the overall body of evidence assigned within the primary systematic review was adopted. 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, the Evidence-based Practice Center approach was adapted to assign an overall strength of evidence grade based on consensus discussions involving at least 2 reviewers.[10]

[c] 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.

[d] Sensitivity analysis including only those studies judged to have a low risk of bias did not affect 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.

[e] 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 (odds ratio, 1.52 [95% 1.29-1.78]) and 16.2% randomized to bupropion (odds ratio, 1.45 [95% CI, 1.24-1.70]).[116]

[f] 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.

[g] Total number of studies and observations not estimated.

[h] Despite the relatively limited number of reviews that reported harms related to interventions, it appears likely that there are no serious harms related to combined pharmacotherapy and behavioral counseling interventions or behavioral counseling alone for tobacco cessation.

In contrast to the robust evidence on pharmacotherapy and behavioral interventions for smoking cessation, evidence on the use of e-cigarettes as an intervention to quit conventional smoking is lacking (Table 3). No studies on the use of e-cigarettes as tobacco cessation interventions reported health outcomes, and few trials reported on the potential adverse events of e-cigarette use when used in atttempts to quit smoking. This is particularly concerning given the apparent longer-term use of e-cigarettes for cessation compared to pharmacotherapy in addition to the recent outbreak of e-cigarette, or vaping, product use–associated lung injury.[118] Furthermore, there is lack of long-term epidemiologic studies and large clinical trials examining the associations between e-cigarette use and morbidity and mortality, especially in the long term.[119]

Although this review was scoped to include interventions focused on quitting any tobacco product, most published trials have targeted (and reported) quitting combustible cigarette use. More research is needed on interventions to help people quit other tobacco products such as cigars, smokeless tobacco, and e-cigarettes. Given the high prevalence of dual use of combustible and electronic cigarettes,[120] there is a need for research on interventions to help dual users of conventional cigarettes and e-cigarettes quit both products, as well as research on potential relapse back to cigarette use among former smokers who use e-cigarettes.

Limitations

The primary limitation of the evidence report relates to the overview of reviews approach. The comprehensiveness of the overview of reviews is inevitably limited by the recency and quality of the source reviews. Although most of the reviews included evidence at least through 2015, there may be evidence on specific 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, it appears unlikely that any new trials, regardless of their sample size and effect estimates, would have substantial bearing on the overall results of this overview of reviews.

Conclusions

There is strong evidence that a range of pharmacologic and behavioral interventions, both individually and in combination, are effective in increasing smoking cessation in nonpregnant adults. In pregnancy, behavioral interventions are effective for smoking cessation, but data are limited on the use of pharmacotherapy for smoking cessation. Data on the effectiveness and safety of electronic cigarettes for smoking cessation among adults are also limited and results are inconsistent.

ARTICLE INFORMATION

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Author Contributions: Dr Patnode had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Patnode, Henderson, Coppola, Melnikow.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Patnode, Coppola.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Patnode.
Administrative, technical, or material support: Henderson, Coppola, Melnikow, Durbin, Thomas.
Supervision: Patnode, Henderson, Melnikow.

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Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional peer review after submission to *JAMA*.

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