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

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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 (NRT), bupropion hydrochloride sustained release [bupropion], and varenecline (RR, 2.27 [CI, 2.02 to 2.55]) were also effective for smoking cessation.

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.

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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

<table>
<thead>
<tr>
<th>Study, Year (Reference), by Intervention Type</th>
<th>Quality Rating</th>
<th>Specific Intervention or Population</th>
<th>Last Search Date</th>
<th>Included Studies, n</th>
<th>Health Outcomes</th>
<th>Cessation</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral support and counseling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Stead et al, 2013 (58)*</td>
<td>Good</td>
<td>Physician advice</td>
<td>January 2013</td>
<td>42</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Rice and Stead, 2013 (55)*</td>
<td>Good</td>
<td>Nursing interventions</td>
<td>June 2013</td>
<td>49</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Carr et al, 2012 (26)</td>
<td>Good</td>
<td>Interventions in dental settings</td>
<td>November 2011</td>
<td>14</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cahill et al, 2010 (25)</td>
<td>Good</td>
<td>Stage-based interventions</td>
<td>August 2010</td>
<td>41</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hettema and Hendricks, 2010 (38f)</td>
<td>Fair</td>
<td>Motivational interviewing</td>
<td>June 2008</td>
<td>23</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lai et al, 2010 (43)</td>
<td>Good</td>
<td>Health professional advice</td>
<td>April 2009</td>
<td>14</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Bodnar and Dean, 2009 (23)</td>
<td>Fair</td>
<td>Counseling</td>
<td>NR</td>
<td>30</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Mottillo et al, 2009 (50)</td>
<td>Fair</td>
<td>Counseling</td>
<td>August 2007</td>
<td>50</td>
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<td>✓</td>
<td></td>
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<tr>
<td><strong>Behavioral support as an adjunct to pharmacotherapy</strong></td>
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</tr>
<tr>
<td>Stead and Lancaster, 2012 (61)*</td>
<td>Good</td>
<td>Behavioral support as an adjunct to pharmacotherapy</td>
<td>July 2012</td>
<td>38</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann-Boyce et al, 2014 (37)*</td>
<td>Good</td>
<td>Print-based self-help materials</td>
<td>April 2014</td>
<td>74</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Stead et al, 2013 (60)*</td>
<td>Good</td>
<td>Telephone counseling</td>
<td>May 2013</td>
<td>77</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Tzelepis et al, 2011 (66)</td>
<td>Fair</td>
<td>Proactive telephone counseling</td>
<td>December 2008</td>
<td>24</td>
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<td></td>
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<tr>
<td>Whittaker et al, 2012 (71)*</td>
<td>Fair</td>
<td>Mobile telephone</td>
<td>May 2012</td>
<td>5</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Civljak et al, 2013 (31)*</td>
<td>Good</td>
<td>Internet-based</td>
<td>April 2013</td>
<td>28</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Brown, 2013 (24)</td>
<td>Fair</td>
<td>Internet-based, young adults</td>
<td>February 2011</td>
<td>8</td>
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<tr>
<td>Hutton et al, 2011 (41)</td>
<td>Good</td>
<td>Internet-based</td>
<td>December 2009</td>
<td>60</td>
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<td>✓</td>
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</tr>
<tr>
<td>Myung et al, 2009 (51)</td>
<td>Good</td>
<td>Internet- or computer-based</td>
<td>August 2008</td>
<td>22</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Shahab and McEwen, 2009 (56)</td>
<td>Fair</td>
<td>Internet-based</td>
<td>December 2008</td>
<td>11</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Biomedical risk assessment</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size et al, 2012 (22)*</td>
<td>Good</td>
<td>Biomedical risk assessment</td>
<td>June 2012</td>
<td>15</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ussher et al, 2014 (67)*</td>
<td>Fair</td>
<td>Exercise</td>
<td>May 2014</td>
<td>20</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Complementary and alternative therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White et al, 2014 (70)*</td>
<td>Good</td>
<td>Acupuncture</td>
<td>October 2013</td>
<td>38</td>
<td></td>
<td>✓</td>
<td></td>
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<tr>
<td>Di et al, 2014 (33)</td>
<td>Good</td>
<td>Acupuncture</td>
<td>January 2013</td>
<td>25</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cheng et al, 2012 (30)</td>
<td>Fair</td>
<td>Acupoint stimulation</td>
<td>March 2011</td>
<td>20</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tahiri et al, 2012 (63)</td>
<td>Fair</td>
<td>Alternative therapies</td>
<td>December 2010</td>
<td>14</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Barnes et al, 2010 (21)*</td>
<td>Good</td>
<td>Hypnotherapy</td>
<td>July 2010</td>
<td>11</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>NRT</strong></td>
<td>Good</td>
<td>NRT</td>
<td>July 2012</td>
<td>150</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>Good</td>
<td>Varenicline (nicotine receptor partial agonists)</td>
<td>December 2011</td>
<td>20</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td><strong>Varenicline harms</strong></td>
<td>Good</td>
<td>Varenicline harms</td>
<td>September 2011</td>
<td>22</td>
<td></td>
<td>✓</td>
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<td><strong>Continued on following page</strong></td>
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</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Study, Year (Reference), by Intervention Type</th>
<th>Quality Rating</th>
<th>Specific Intervention or Population</th>
<th>Last Search Date</th>
<th>Included Studies, n</th>
<th>Health Outcomes</th>
<th>Cessation Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults: combined pharmacotherapy and behavioral interventions (1 systematic review; 1 primary review)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stead and Lancaster, 2012 (57)*</td>
<td>Good</td>
<td>Combined pharmacotherapy and behavioral support</td>
<td>July 2012</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults: electronic nicotine delivery systems (2 RCTs)†</td>
<td></td>
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</tr>
<tr>
<td>Bullen et al, 2013 (74)</td>
<td>Fair</td>
<td>Electronic cigarettes</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caponnetto et al, 2013 (75)</td>
<td>Fair</td>
<td>Electronic cigarettes</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women: behavioral interventions (6 systematic reviews; 1 primary review)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chamberlain et al, 2013 (28)*</td>
<td>Good</td>
<td>Behavioral interventions among pregnant women</td>
<td>March 2013</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filion et al, 2011 (35)</td>
<td>Fair</td>
<td>Behavioral interventions among pregnant women</td>
<td>June 2010</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hettema and Hendricks, 2010 (38)‡</td>
<td>Fair</td>
<td>Behavioral interventions among pregnant women</td>
<td>June 2008</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likis et al, 2014 (44)</td>
<td>Good</td>
<td>Pharmacotherapy and behavioral interventions among pregnant women</td>
<td>January 2013</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su and Buttenheim, 2013 (62)</td>
<td>Fair</td>
<td>Pharmacotherapy and behavioral interventions among pregnant women</td>
<td>December 2012</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bondurant and Wedge, 2009 (76)</td>
<td>Good</td>
<td>Pharmacotherapy and behavioral interventions among pregnant women</td>
<td>June 2008</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women: pharmacotherapy interventions (6 systematic reviews; 1 primary review)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Coleman et al, 2012 (32)*</td>
<td>Good</td>
<td>Pharmacotherapy among pregnant women</td>
<td>March 2012</td>
<td>7§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myung et al, 2012 (52)</td>
<td>Good</td>
<td>Pharmacotherapy among pregnant women</td>
<td>June 2011</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likis et al, 2014 (44)</td>
<td>Good</td>
<td>Pharmacotherapy and behavioral interventions among pregnant women</td>
<td>January 2013</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su and Buttenheim, 2013 (62)</td>
<td>Fair</td>
<td>Pharmacotherapy and behavioral interventions among pregnant women</td>
<td>December 2012</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bondurant and Wedge, 2009 (76)</td>
<td>Good</td>
<td>Pharmacotherapy and behavioral interventions among pregnant women</td>
<td>June 2008</td>
<td>72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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).
### Table 2. Summary of Evidence for the General Adult Population

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Included Reviews, n</th>
<th>Summary of Findings</th>
<th>Consistency</th>
<th>Major Limitations</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral</td>
<td>1</td>
<td>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.</td>
<td>NA</td>
<td>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.</td>
<td>1 trial conducted among male civil servants aged 40-59 y in the United Kingdom with high risk for cardiorespiratory disease. Intervention took place in the 1970s.</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Combined pharmacotherapy and behavioral</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ENDS</td>
<td>0 RCTs</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Cessation outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral</td>
<td>26</td>
<td>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%-76%). 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.</td>
<td>Consistent</td>
<td>Individual trials may be represented in &gt;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.</td>
<td>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.</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>6</td>
<td>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.</td>
<td>Consistent</td>
<td>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 pharmaceutical companies (particularly for varenicline), the magnitude of the effects may be smaller than estimates suggest.</td>
<td>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.</td>
</tr>
</tbody>
</table>

Continued on following page
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Included Reviews, ( n )</th>
<th>Summary of Findings</th>
<th>Consistency</th>
<th>Major Limitations</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined pharmacotherapy and behavioral</td>
<td>1</td>
<td>Combined pharmacotherapy and behavioral interventions increase cessation rates by 70%–100% compared with no or minimal treatment</td>
<td>Consistent</td>
<td>May be risk of bias due to lack of blinding of participants.</td>
<td>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.</td>
</tr>
<tr>
<td>ENDS</td>
<td>2 RCTs</td>
<td>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.</td>
<td>Consistent</td>
<td>Insufficient statistical power to detect differences and differential high loss to follow-up in both trials (22%–40%).</td>
<td>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.</td>
</tr>
<tr>
<td>AEs</td>
<td></td>
<td></td>
<td>NA</td>
<td>Only 2 reviews assessed AEs related to behavioral interventions; 1 found no studies that reported AEs.</td>
<td>Limited evidence on harms limits applicability.</td>
</tr>
<tr>
<td>Behavioral</td>
<td>2</td>
<td>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.</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>8</td>
<td>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.</td>
<td>Consistent</td>
<td>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.</td>
<td>Likely applicable across settings and populations.</td>
</tr>
</tbody>
</table>
suggested that more intensive advice offered a significant advantage (RR, 1.37 [CI, 1.20 to 1.56]; 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, 1.50 [CI, 1.53 to 1.68]; 117 trials; I² = 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; I² = 34%; n = 46,664) (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]; I² = 0%; 17 trials; n = 77,25) (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]; I² = 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 biochemical 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>
<thead>
<tr>
<th>Intervention</th>
<th>Included Reviews, n</th>
<th>Summary of Findings</th>
<th>Consistency</th>
<th>Major Limitations</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral</td>
<td>3</td>
<td>Statistically significant benefit of behavioral interventions on mean birthweight, low birthweight, and preterm birth vs. usual care or control.</td>
<td>Consistent</td>
<td>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.</td>
<td>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).</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>4</td>
<td>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.</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cessation outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral</td>
<td>6</td>
<td>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.</td>
<td>Consistent</td>
<td>Limited information on the women approached for participation who declined and low participation rates.</td>
<td>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).</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>5</td>
<td>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.</td>
<td>Consistent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 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

<table>
<thead>
<tr>
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<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral</td>
<td>1</td>
<td>No serious AEs reported.</td>
<td>NA</td>
<td>Inconsistent data collection across trials; most reliant on passive reporting.</td>
<td>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).</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>5</td>
<td>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.</td>
<td>NA</td>
<td>Few trials of NRT, and not all reported consistently on health outcomes and AEs.</td>
<td>AE = adverse event; NA = not applicable; NRT = nicotine replacement therapy; SR = sustained release.</td>
</tr>
</tbody>
</table>
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).

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Interventions for Smoking Cessation

.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


Review

Interventions for Smoking Cessation


47. Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO. Adverse events associated with nicotine replacement therapy (NRT) for smoking ces-
Interventions for Smoking Cessation

Appendix Figure 1. Analytic framework.

KQ1

Intervention for smoking cessation (counseling and/or pharmacotherapy)

KQ2

Behavioral outcomes

Smoking cessation

Adverse events

KQ3

Health outcomes

Mortality

Morbidity

Other

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.**

![Diagram showing the evidence search and selection process](Diagram.png)

- **Citations identified through literature database search** (n = 1141)
- **Duplicates removed** (n = 503)
- **Citations screened after duplicates removed** (n = 638)
- **Citations excluded at title/abstract stage** (n = 524)
- **Full-text systematic reviews assessed for eligibility** (n = 114)*
  - **Full-text evaluation of systematic reviews for adults** (n = 851)
  - **Full-text evaluation of systematic reviews for pregnant women** (n = 161)
  - **Full-text evaluation of systematic reviews for mental health** (n = 15)
  - **Excluded** (n = 43)
    - Aim: 3
    - Design/scope: 21
    - Population: 0
    - Intervention: 7
    - Setting: 0
    - Outcomes: 6
    - Non-English: 0
    - Quality: 6
  - **Excluded** (n = 8)
    - Aim: 0
    - Design/scope: 5
    - Population: 0
    - Intervention: 1
    - Setting: 0
    - Outcomes: 1
    - Non-English: 0
    - Quality: 1
  - **Excluded** (n = 11)
    - Aim: 1
    - Design/scope: 8
    - Population: 0
    - Intervention: 0
    - Setting: 0
    - Outcomes: 1
    - Non-English: 0
    - Quality: 1
  - **Systematic reviews included for adults** (n = 42)†
    - Primary reviews: 18
  - **Systematic reviews included for pregnant women** (n = 8)†
    - Primary reviews: 2
  - **Systematic reviews included for mental health** (n = 4)†
    - Primary reviews: 2

* 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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
<th>Studies, n</th>
<th>Participants, n</th>
<th>Abstinence Measures*</th>
<th>Follow-up, mo†</th>
<th>IG Events, n</th>
<th>IG Participants, n</th>
<th>IG Cessation Rate, %‡</th>
<th>CG Events, n</th>
<th>CG Participants, n</th>
<th>CG Cessation Rate, %‡</th>
<th>Risk Ratio (95% CI)§</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral interventions for smoking cessation</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stead et al, 2013 (58)</td>
<td>Physician advice No advice/usual care</td>
<td>28</td>
<td>22 239</td>
<td>42% CA 36% BV</td>
<td>≥6</td>
<td>1008</td>
<td>12 583</td>
<td>8.0</td>
<td>462</td>
<td>9656</td>
<td>4.8</td>
<td>1.76 (1.58–1.96)</td>
<td>40</td>
</tr>
<tr>
<td>Rice et al, 2013 (55)</td>
<td>Nursing interventions Usual care or minimal intervention</td>
<td>35</td>
<td>17 604</td>
<td>29% CA 77% BV</td>
<td>≥6</td>
<td>1273</td>
<td>9589</td>
<td>13.3</td>
<td>906</td>
<td>8015</td>
<td>11.3</td>
<td>1.29 (1.20-1.39)</td>
<td>50</td>
</tr>
<tr>
<td>Stead and Lancaster, 2013 (61)</td>
<td>Behavioral support as an adjunct to pharmacotherapy Pharmacotherapy (any)</td>
<td>39</td>
<td>15 506</td>
<td>28% CA 79% BV</td>
<td>≥6</td>
<td>1640</td>
<td>7659</td>
<td>21.4</td>
<td>1438</td>
<td>7847</td>
<td>18.3</td>
<td>1.16 (1.09-1.24)</td>
<td>3</td>
</tr>
<tr>
<td>Hartmann-Boye et al, 2014 (37)</td>
<td>Tailored print-based self-help materials Control (various)</td>
<td>32</td>
<td>40 890</td>
<td>72% CA 28% BV</td>
<td>≥6</td>
<td>1502</td>
<td>21 017</td>
<td>7.1</td>
<td>1144</td>
<td>19 873</td>
<td>5.8</td>
<td>1.28 (1.18-1.37)</td>
<td>32</td>
</tr>
<tr>
<td>Nontailored print-based self-help materials Control (various)</td>
<td>33</td>
<td>29 495</td>
<td>42% CA 55% BV</td>
<td>≥6</td>
<td>1080</td>
<td>15 635</td>
<td>6.9</td>
<td>891</td>
<td>13 860</td>
<td>6.4</td>
<td>1.06 (0.98-1.16)</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Stead et al, 2013 (50)</td>
<td>Proactive telephone counseling among quit line callers Control (various)</td>
<td>12</td>
<td>30 182</td>
<td>75% CA 25% BV</td>
<td>≥6</td>
<td>1980</td>
<td>18 428</td>
<td>10.7</td>
<td>895</td>
<td>11 754</td>
<td>7.6</td>
<td>1.41 (1.20-1.66)</td>
<td>NR</td>
</tr>
<tr>
<td>Proactive telephone counseling (no quit line) Control (various)</td>
<td>32</td>
<td>30 246</td>
<td>33% CA 67% BV</td>
<td>≥6</td>
<td>2031</td>
<td>15 478</td>
<td>13.1</td>
<td>1433</td>
<td>14 768</td>
<td>9.7</td>
<td>1.27 (1.20-1.36)</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Whitaker et al, 2012 (71)</td>
<td>Mobile telephone interventions Civlak et al, 2013 (31)</td>
<td>5</td>
<td>9100</td>
<td></td>
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<tr>
<td>Internet-based interventions No treatment or other non-Internet-based treatments Control (various)</td>
<td>23</td>
<td>&gt;45 000</td>
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</tr>
<tr>
<td>Bize et al, 2012 (22)</td>
<td>Biomedical risk assessment Control (various)</td>
<td>15</td>
<td>8115</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Usher et al, 2014 (67)</td>
<td>Exercise alone or as adjunct to interventions for smoking cessation Intervention for smoking cessation alone or usual care</td>
<td>20</td>
<td>5870</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White et al, 2014 (70)</td>
<td>Acupuncture Sham acupuncture</td>
<td>9</td>
<td>1892</td>
<td>33% CA 33% BV</td>
<td>6-12</td>
<td>122</td>
<td>997</td>
<td>12.2</td>
<td>97</td>
<td>895</td>
<td>10.8</td>
<td>1.10 (0.86-1.40)</td>
<td>23</td>
</tr>
<tr>
<td>Barnes et al, 2010 (21)</td>
<td>Hypnotherapy Brief advice/advice</td>
<td>5</td>
<td>363</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Pharmacotherapy interventions for smoking cessation</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Stead et al, 2012 (59)</td>
<td>NRT, all forms Placebo or no NRT¶</td>
<td>117</td>
<td>51 265</td>
<td>57% CA 43% BV</td>
<td>≥6</td>
<td>4704</td>
<td>27 258</td>
<td>17.3</td>
<td>2466</td>
<td>24 007</td>
<td>10.3</td>
<td>1.60 (1.53-1.68)</td>
<td>30</td>
</tr>
<tr>
<td>NRT, gum Placebo or no NRT¶</td>
<td>56</td>
<td>22 581</td>
<td>55% CA 45% BV</td>
<td>≥6</td>
<td>1732</td>
<td>10 596</td>
<td>16.3</td>
<td>1196</td>
<td>11 985</td>
<td>10.0</td>
<td>1.49 (1.40-1.60)</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>NRT, patch Placebo or no NRT¶</td>
<td>43</td>
<td>19 586</td>
<td>58% CA 42% BV</td>
<td>≥6</td>
<td>1873</td>
<td>11 746</td>
<td>15.9</td>
<td>766</td>
<td>7840</td>
<td>9.8</td>
<td>1.64 (1.52-1.78)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>NRT, tablets/lozenges Placebo or no NRT¶</td>
<td>7</td>
<td>3405</td>
<td>29% CA 71% BV</td>
<td>≥6</td>
<td>337</td>
<td>1808</td>
<td>18.6</td>
<td>134</td>
<td>1597</td>
<td>8.4</td>
<td>1.95 (1.61-2.36)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Two forms of NRT (dual) One form of NRT</td>
<td>9</td>
<td>4664</td>
<td>67% CA 33% BV</td>
<td>≥6</td>
<td>368</td>
<td>1785</td>
<td>20.6</td>
<td>448</td>
<td>2879</td>
<td>15.6</td>
<td>1.34 (1.18-1.51)</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

Continued on following page
**Appendix Table 2—Continued**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
<th>Studies, n</th>
<th>Participants, n</th>
<th>Abstinence Measures*</th>
<th>Follow-up, mo†</th>
<th>IG Events, n</th>
<th>IG Participants, n</th>
<th>IG Cessation Rate, %‡</th>
<th>CG Events, n</th>
<th>CG Participants, n</th>
<th>CG Cessation Rate, %‡</th>
<th>Risk Ratio (95% CI)§</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes et al, 2014 (40)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>Placebo or no bupropion SR**</td>
<td>44</td>
<td>13,728</td>
<td>77% CA 95% BV</td>
<td>≥6</td>
<td>1507</td>
<td>7646</td>
<td>19.7</td>
<td>701</td>
<td>6082</td>
<td>11.5</td>
<td>1.62 (1.49–1.76)</td>
<td>18</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>Placebo or no bupropion SR**</td>
<td>17</td>
<td>3862</td>
<td>59% CA 100% BV</td>
<td>6</td>
<td>483</td>
<td>2202</td>
<td>21.9</td>
<td>200</td>
<td>1660</td>
<td>12.0</td>
<td>1.69 (1.45–1.97)</td>
<td>0</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>Placebo or no bupropion SR**</td>
<td>27</td>
<td>9866</td>
<td>81% CA 93% BV</td>
<td>12</td>
<td>1024</td>
<td>5444</td>
<td>18.8</td>
<td>501</td>
<td>4422</td>
<td>11.3</td>
<td>1.59 (1.44–1.76)</td>
<td>39</td>
</tr>
<tr>
<td>Cahill et al, 2012 (73)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>Placebo††</td>
<td>14</td>
<td>6166</td>
<td>100% CA 100% BV</td>
<td>≥6</td>
<td>954</td>
<td>3412</td>
<td>28.0</td>
<td>331</td>
<td>2754</td>
<td>12.0</td>
<td>2.27 (2.02–2.55)</td>
<td>63</td>
</tr>
</tbody>
</table>

**Combined interventions for smoking cessation**

| 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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design, Country</th>
<th>Sample Size, n</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes for Smoking Cessation</th>
<th>Other Outcomes</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullen et al, 2013 (74)</td>
<td>RCT; New Zealand</td>
<td>Total: 657</td>
<td>Aged ≥18 y, had smoked ≥10 cigarettes per day for at least the past year, wanted to stop smoking</td>
<td>IG: Elusion electronic cigarette (16 mg nicotine) + voluntary quit line behavioral support Duration: From 1 wk before until 12 wk after chosen cessation date</td>
<td>CG1: NRT patch (21-mg nicotine/24 h) CG2: placebo electronic cigarettes + voluntary quit line behavioral support</td>
<td>Continuous abstinence at 6 mo after cessation date (allowing ≤5 cigarettes); biochemically verified: IG: 7.3%* CG1: 5.8% CG2: 4.1%</td>
<td>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)‡</td>
<td>No serious events in any groups were related to product use</td>
</tr>
<tr>
<td>Caponnetto et al, 2013 (75)</td>
<td>RCT; Italy</td>
<td>Total: 300</td>
<td>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</td>
<td>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)</td>
<td>Categoria 401 Electronic cigarette CG: 12 wk of no-nicotine cartridges used ad libitum</td>
<td>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: 11.0%§ IG2: 9.0% CG: 4.0%</td>
<td>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</td>
<td>No difference in frequency of AEs among study groups at each time point</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
<th>Studies, n</th>
<th>Participants, n</th>
<th>Follow-up‡</th>
<th>IG Events, n</th>
<th>IG Participants, n</th>
<th>CG Events, n</th>
<th>CG Participants, n</th>
<th>RR§ or Mean Difference (95% CI)</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: mean birthweight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All behavioral interventions</td>
<td></td>
<td>Usual care or control</td>
<td>19</td>
<td>9,859</td>
<td>21% PPA 66% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>NA</td>
<td>4948</td>
<td>NA</td>
<td>4911</td>
</tr>
<tr>
<td>Counseling</td>
<td></td>
<td>Usual care or control</td>
<td>12</td>
<td>5,392</td>
<td>17% PPA 67% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>NA</td>
<td>2619</td>
<td>NA</td>
<td>2773</td>
</tr>
<tr>
<td><strong>Outcome: low birthweight (&lt; 2500 g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All behavioral interventions</td>
<td></td>
<td>Usual care or control</td>
<td>14</td>
<td>8,562</td>
<td>14% PPA 79% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>304</td>
<td>4298</td>
<td>381</td>
<td>4264</td>
</tr>
<tr>
<td>Counseling</td>
<td></td>
<td>Usual care or control</td>
<td>8</td>
<td>4,339</td>
<td>13% PPA 88% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>151</td>
<td>2090</td>
<td>200</td>
<td>2249</td>
</tr>
<tr>
<td><strong>Outcome: preterm birth (&lt; 37 wk)</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All behavioral interventions</td>
<td></td>
<td>Usual care or control</td>
<td>14</td>
<td>7,852</td>
<td>29% PPA 71% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>251</td>
<td>3992</td>
<td>307</td>
<td>3860</td>
</tr>
<tr>
<td>Counseling</td>
<td></td>
<td>Usual care or control</td>
<td>8</td>
<td>3,447</td>
<td>25% PPA 85% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>99</td>
<td>1672</td>
<td>117</td>
<td>1775</td>
</tr>
<tr>
<td><strong>Outcome: stillbirth</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>All behavioral interventions</td>
<td></td>
<td>Usual care or control</td>
<td>7</td>
<td>5,414</td>
<td>0% PPA 100% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>38</td>
<td>2676</td>
<td>31</td>
<td>2738</td>
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<tr>
<td>Counseling</td>
<td></td>
<td>Usual care or control</td>
<td>5</td>
<td>2,454</td>
<td>0% PPA 100% BV</td>
<td>Late pregnancy, including during hospitalization for delivery</td>
<td>16</td>
<td>1197</td>
<td>14</td>
<td>1257</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
<th>Studies, n</th>
<th>Participants, n</th>
<th>Abstinence Measures*</th>
<th>Follow-up†</th>
<th>IG Events, n</th>
<th>IG Participants, n</th>
<th>IG Cessation Rate, %‡</th>
<th>CG Events, n</th>
<th>CG Participants, n</th>
<th>CG Cessation Rate, %‡</th>
<th>Risk Ratio (95% CI)§</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamberlain et al, 2013 (28)</td>
<td>Any behavioral interventions]]</td>
<td>Usual care or control</td>
<td>70</td>
<td>21,948</td>
<td>0% CA 79% BV Late pregnancy, including during hospitalization for delivery</td>
<td>1691</td>
<td>11,111</td>
<td>15.2</td>
<td>1213</td>
<td>10,837</td>
<td>11.2</td>
<td>1.45 (1.27–1.64)</td>
<td>60</td>
</tr>
<tr>
<td>Counseling</td>
<td>Usual care or control</td>
<td>45</td>
<td>17,681</td>
<td>0% CA 82% BV Late pregnancy, including during hospitalization for delivery</td>
<td>1283</td>
<td>88,30</td>
<td>14.5</td>
<td>992</td>
<td>88,51</td>
<td>11.2</td>
<td>1.37 (1.17–1.59)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Social support</td>
<td>Usual care or control</td>
<td>10</td>
<td>1,683</td>
<td>0% CA 70% BV Late pregnancy, including during hospitalization for delivery</td>
<td>168</td>
<td>845</td>
<td>19.9</td>
<td>128</td>
<td>83,8</td>
<td>15.3</td>
<td>1.29 (0.97–1.73)</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Coleman et al, 2012 (32)</td>
<td>NRT, all forms¶</td>
<td>Placebo</td>
<td>4</td>
<td>1,520</td>
<td>25% CA 100% BV Late pregnancy, including during hospitalization for delivery</td>
<td>93</td>
<td>7,62</td>
<td>12.2</td>
<td>71</td>
<td>758</td>
<td>9.4</td>
<td>1.27 (0.95–1.69)</td>
<td>0</td>
</tr>
<tr>
<td>Coleman et al, 2012 (32) + Berlin study identified in bridge search (77)</td>
<td>NRT, all forms**</td>
<td>Placebo</td>
<td>5††</td>
<td>1,922</td>
<td>40% CA 100% BV Late pregnancy, including during hospitalization for delivery</td>
<td>104</td>
<td>9,65</td>
<td>10.8</td>
<td>81</td>
<td>957</td>
<td>8.5</td>
<td>1.24 (0.95–1.64)</td>
<td>0</td>
</tr>
</tbody>
</table>

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.
†† Includes 4 trials identified in the Coleman review and 1 additional trial included from our bridge search.