



Comparative Effectiveness of Smoking Cessation Treatments for Patients With Depression: A Systematic Review and Meta-analysis of the Evidence

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PREFACE

HSR&D's Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to VA managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

HSR&D provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, an ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of HSR&D field-based investigators, VA Patient Care Services, Office of Quality and Performance, and VISN Clinical Management Officers. The Steering Committee provides program oversight and guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EVIDENCE REPORT

INTRODUCTION

Tobacco smoking is the single greatest preventable cause of disease in the United States.^{1,2} Half of all American smokers who fail to quit will die of a smoking-related illness.³ Cigarette use is higher among Americans with depression than in the general U.S. population.⁴ Persons with depression are about twice as likely (45% versus 22%) to be current smokers than are individuals who are not depressed,⁵ and smokers are more likely to have a history of depression.^{6,7} Moreover, veterans have higher rates of depression and smoking compared to the general population.⁸⁻¹²

Several hypotheses have been offered to explicate the association between smoking and depression, including mood-enhancing effects of nicotine^{13,14} and common genetic and environmental factors. Depression also appears to be an important factor in smoking cessation.¹⁵⁻²⁰ Smokers who are depressed are more likely to relapse from a quit attempt, have higher nicotine dependence, suffer negative mood symptoms from withdrawal, and suffer greater smoking-related morbidity and mortality than the general population of smokers.^{17,18,21-24}

Smokers with depression are highly motivated to quit smoking.^{7,25} One study found that 79% of smokers with depression intended to quit, with 24% ready to make a quit attempt in the next month.²⁶ Despite the complex relationship between tobacco use and depression, smokers with depression should be offered cessation services.^{27,28} Several evidence-based smoking cessation intervention strategies exist for the general population of smokers.²⁹⁻³⁵ All forms of nicotine replacement therapy (NRT) (e.g., gum, transdermal patch, inhaler, lozenges) augment successful quit attempts, increasing quit rates by as much as 50 to 70%.³⁵ Also, use of some antidepressants (i.e., bupropion, nortriptyline) can double the chances of smoking cessation, and this effect seems independent of the antidepressive effects of these medications.³⁶ For behavioral interventions, there is a strong dose-response relationship between treatment intensity and smoking cessation rates.³⁷ More intensive interventions, measured by total contact time, are associated with increased abstinence rates. For example, smoking cessation counseling improves quit attempts over self-help aids and other less intensive therapies.^{29,33,34,38} Combining behavioral interventions with pharmacotherapy increases quit attempts over each therapy delivered alone and is considered the gold standard of care for effective smoking cessation treatment.^{29,37,39}

Gender, depression status (e.g., history positive, depression symptom severity), and content delivery timing (i.e., sequential, concurrent) may differentially impact the effectiveness of smoking cessation intervention efforts for smokers with depression. When trying to quit smoking, women who are depressed may experience more difficulty with withdrawal symptoms and, consequently, higher rates of smoking relapse to alleviate withdrawal symptoms compared to their male smoker counterparts.⁴⁰ Level of depressive symptoms or depression type may influence patients' ability to make and maintain quit attempts.^{17,18,22} Also, smokers with depression may benefit from smoking cessation programs that target both depression symptoms and tobacco use. However, it is not known if these two conditions should be treated concurrently or sequentially. For example, it is not known if treating depression first influences smoking cessation treatment effectiveness. Treating depression first may lead to greater treatment adherence and, consequently, better cessation rates. It is plausible but unstudied. Smokers with psychiatric comorbidities may benefit from combined behavioral counseling and

pharmacotherapy with longer therapeutic smoking cessation approaches (i.e., exceeding 8 to 12 weeks) to reduce likelihood of dropout and depression relapse.^{27,41} However, no systematic reviews have synthesized the comparative effectiveness of smoking cessation strategies for persons with depressive symptoms. Many unanswered questions remain about how effective smoking cessation interventions are for adults with depression.

METHODS

TOPIC DEVELOPMENT

This review was commissioned by the Department of Veterans Affairs' Evidence-based Synthesis Program. The topic was selected after a formal topic nomination and prioritization process that included representatives from the Office of Mental Health Services, Health Services Research and Development, the Mental Health QUERI, and the Office of Mental Health and Primary Care Integration. The key research questions for this review were developed and refined after preliminary review of published peer-reviewed literature and consultation with VA and non-VA experts to select the patients and subgroups, interventions, outcomes, and settings addressed in this review.

The final key questions were as follows:

Key Question 1: For patients with a history of a depressive disorder or current significant depressive symptoms, what is the comparative effectiveness of different smoking cessation strategies on smoking abstinence rates?

Key Question 2: For patients with a history of a depressive disorder or current significant depressive symptoms, are there differential effects of smoking cessation strategies by depression status (i.e., history of MDD, current depressive symptoms, current MDD)?

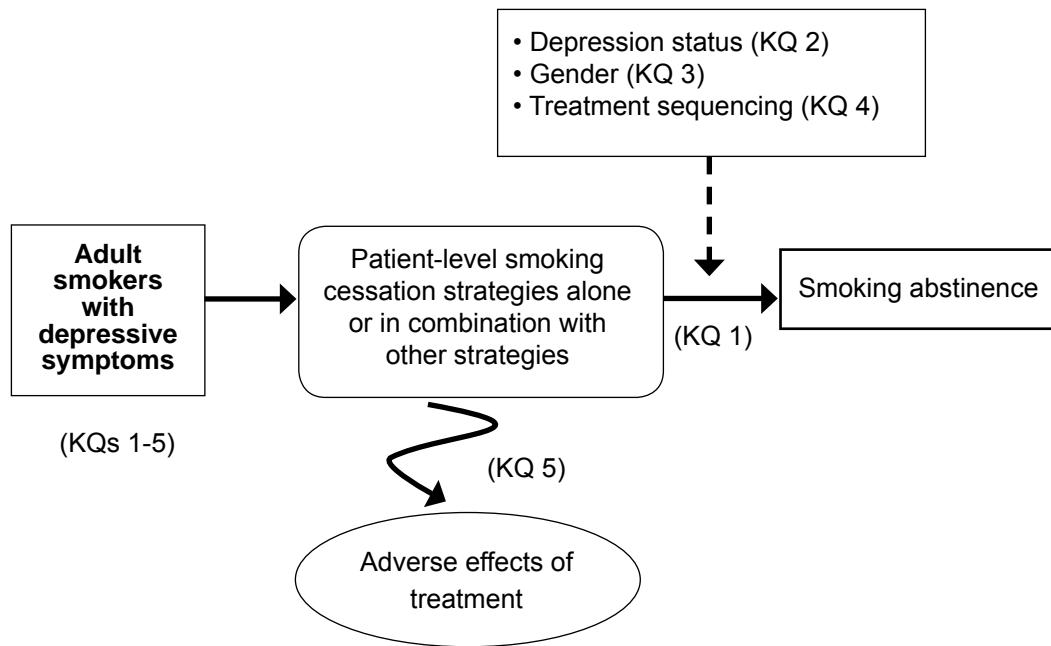
Key Question 3: For patients with a history of a depressive disorder or current significant depressive symptoms, are there differential effects of smoking cessation strategies by gender?

Key Question 4: For patients with a history of a depressive disorder or current significant depressive symptoms, does treatment effectiveness differ by whether smoking cessation/depression treatments are delivered concurrently or sequentially?

Key Question 5: What is the nature and frequency of adverse effects of smoking cessation treatments in patients with a history of a depressive disorder or current significant depressive symptoms?

We developed and followed a standard protocol for all steps of this review. Our approach was guided by the analytic framework shown in Figure 1.

Figure 1. Analytic Framework



SEARCH STRATEGY

We searched for English-language publications in MEDLINE (via PubMed), Embase, PsycINFO, and the Cochrane Library from database inception through March 10, 2010. We developed search strategies in consultation with a master librarian. The search terms and MeSH headings for the search strategies appear in Appendix A. We supplemented electronic searching by examining the bibliographies of included studies.

STUDY SELECTION

Using prespecified inclusion/exclusion criteria, two trained researchers reviewed the list of titles and selected articles for further review. Each article retrieved was reviewed with a brief screening form used to determine eligibility. To be included in our evidence report, a study had to (1) be a randomized controlled trial (RCT), (2) compare two or more smoking cessation interventions or compare intervention to control, and (3) report smoking cessation outcomes in adults with depression. Detailed eligibility criteria are described in Table 1.

Table 1. Summary of Inclusion and Exclusion Criteria

Study characteristic	Inclusion criteria	Exclusion criteria
Study design	RCTs or a secondary data analysis from RCTs of smoking cessation interventions	Non-English language publication, cross-sectional studies
Population	Adults age 18 and over with a history of a depressive disorder or current significant depressive symptoms ^a	Pregnant women, adolescents, postpartum depression, depressive symptoms secondary to another primary condition (e.g., substance abuse, schizophrenia)
Interventions	Any patient-level smoking cessation strategies (e.g., self-help, quit lines, physician or brief advice, behavioral counseling, pharmacologic therapies) alone or in combination with other strategies	Policy-level interventions (e.g., smoking bans), mass media campaigns
Comparators	Active comparators or control (e.g., usual care or placebo)	None
Setting	Outpatient (e.g., mental health clinics, primary care) or delivered through remote communication technologies (e.g., telephone, Web)	Hospital-based (inpatient) interventions
Outcome	KQs 1-4: Smoking abstinence reported at \geq 3 months postrandomization KQ 5: Adverse effects including behavioral symptoms, increased anxiety, depression ^b	Relapse prevention ^c

^aWe define significant depressive symptoms as meeting a designated threshold on a validated assessment instrument (e.g., CES-D, BDI).

^bWe considered depression as an adverse effect when participants moved from depressive symptoms to a depressive disorder, or when the intervention arm showed significantly more depressive symptoms compared to a decrease in symptoms in the comparator condition.

^cIntervention strategies that reduce the likelihood of recent quitters returning to smoking.

Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies-Depression Scale, RCT = randomized controlled trial

DATA ABSTRACTION

A trained researcher abstracted data from published reports into evidence tables; a second reviewer overread the evidence tables. We resolved disagreements by consensus among the first and second reviewer or by obtaining a third reviewer's opinion when consensus could not be reached. We abstracted the following data from included studies: (1) Study design and setting, (2) eligibility criteria, (3) exclusion criteria, (4) sample size, (5) demographics, (6) duration of follow-up, (7) depression clinical category, (8) baseline smoking characteristics (e.g., cigarettes per day, tobacco dependence), (9) method used to assess depression, (10) intervention characteristics (e.g., mode, frequency, dose, core therapy components), (11) outcome measures, (12) results, and (13) adverse effects.

QUALITY ASSESSMENT

We assessed risk of bias using the key quality criteria described in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *General Methods Guide*),⁴² adapted for this specific topic. We abstracted data on adequacy of randomization and allocation concealment, comparability

of groups at baseline, blinding, completeness of follow-up and differential loss to follow-up, whether incomplete data were addressed appropriately, validity of outcome measures, and conflict of interest. Using these data elements, we assigned a summary quality score of Good, Fair, or Poor to individual RCTs.

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included studies, organized by key question and intervention, as appropriate. We critically analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each key question.

When study designs and outcomes reported were similar, we estimated pooled risk ratios with 95% confidence intervals (CIs) by using a random effects model with the Mantel-Haenszel method. For these analyses, we classified each intervention element into the following categories: Antidepressants, nicotine replacement therapy (NRT), brief smoking cessation counseling, behavioral counseling for smoking cessation, or behavioral mood management treatment. We defined brief smoking cessation counseling as counseling that was similar in content to what may be given during a physician visit. We defined behavioral counseling for smoking cessation as multisession individual or group therapy that used behavioral strategies, such as those common in cognitive behavioral therapy (CBT), to influence tobacco use. Behavioral mood management treatment was defined as group or individual counseling intended to influence negative mood and improve depression symptomatology above and beyond standard smoking cessation counseling.

Using these intervention categories, there were sufficient studies to perform meta-analyses for two comparisons: Mood management versus control and antidepressants versus control. Other comparisons were synthesized qualitatively. All studies that were analyzed quantitatively used behavioral counseling for smoking cessation in the intervention and control arms. For the mood management comparison, we subgrouped studies using NRT alone or in combination with antidepressants.

The primary outcome was smoking abstinence without smoking relapse. Smoking abstinence was defined as smoking cessation collected as (1) point prevalence abstinence (e.g., in past 7 days) or (2) extended abstinence (e.g., since quit date or last previous follow-up). We included only one effect size per study. Therefore, we assessed the most distal and rigorous (extended abstinence over point prevalence) outcomes reported and categorized as short-term ($3 < 6$ months) or long-term (≥ 6 months) confirmed by self-report, biochemical validation, or both. Our outcome was informed by outcomes used in the Cochrane Collaborative reviews, which are based on the Russell Standard.⁴³ The U.S. Department of Health and Human Services Tobacco Use and Dependence Guideline Panel recommended a minimum of a 6-month period to assess treatment differences in the longer term.³⁷ Therefore, we used 6 months or longer outcomes for meta-analyses. Abstinence could be assessed by self-report or with biochemical verification.

Two studies^{44,45} used a factorial design to compare pharmacological and behavioral interventions; these comparisons were treated as separate studies in the analyses. We evaluated heterogeneity visually and with the Cochran Q statistic⁴⁶ using a threshold p-value of less than 0.10⁴⁷ and the I² statistic.⁴⁸ We considered I² statistic thresholds of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% to represent between-study heterogeneity that might not be important, moderate,

substantial, or considerable, respectively.⁴⁹ We planned a priori to conduct subgroup analyses by depression status (severity and specific diagnosis), gender, and treatment sequencing, but there were not sufficient studies to conduct these analyses. All analyses were performed using Review Manager 5.0 software (The Cochrane Collaboration, Oxford).

Grading the Evidence for Each Key Question

We graded the strength of evidence for each key question using the principles from the GRADE Working Group.⁵⁰ In brief, this approach assesses the strength of evidence for each critical outcome by considering risk of bias, consistency, directness, precision, and publication bias. Other domains relevant to observational designs were not pertinent to our review. After considering each domain, a summary rating of High, Moderate, Low, or Insufficient strength of evidence was assigned after discussion by two reviewers (Table 2).

Table 2. Definitions for Strength of Evidence Rating

Strength of evidence rating	Definition
High quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Insufficient	Evidence on an outcome is absent or too weak, sparse or inconsistent to estimate an effect

PEER REVIEW

Peer reviewer comments and our responses are presented in Appendix B.

RESULTS

LITERATURE SEARCH AND STUDY CHARACTERISTICS

The combined literature search of PubMed, Embase, PsycINFO, and Cochrane databases, minus duplicates, contained 884 unique citations, of which we excluded 792 after reviewing titles and abstracts. We then conducted full-text reviews of 92 articles and pulled 6 additional papers in order to retrieve supplemental methodological or background information on studies included in the full-text review. Of these 98 papers, we excluded 75. Figure 2 summarizes the literature flow. The 23 included reports encompassed 16 unique trials with a total of 3,553 depressed and nondepressed participants. Table 3 summarizes study characteristics. In studies that included depressed and nondepressed participants, we report information for the depressed subgroup when available.

Figure 2. Literature Flow Diagram

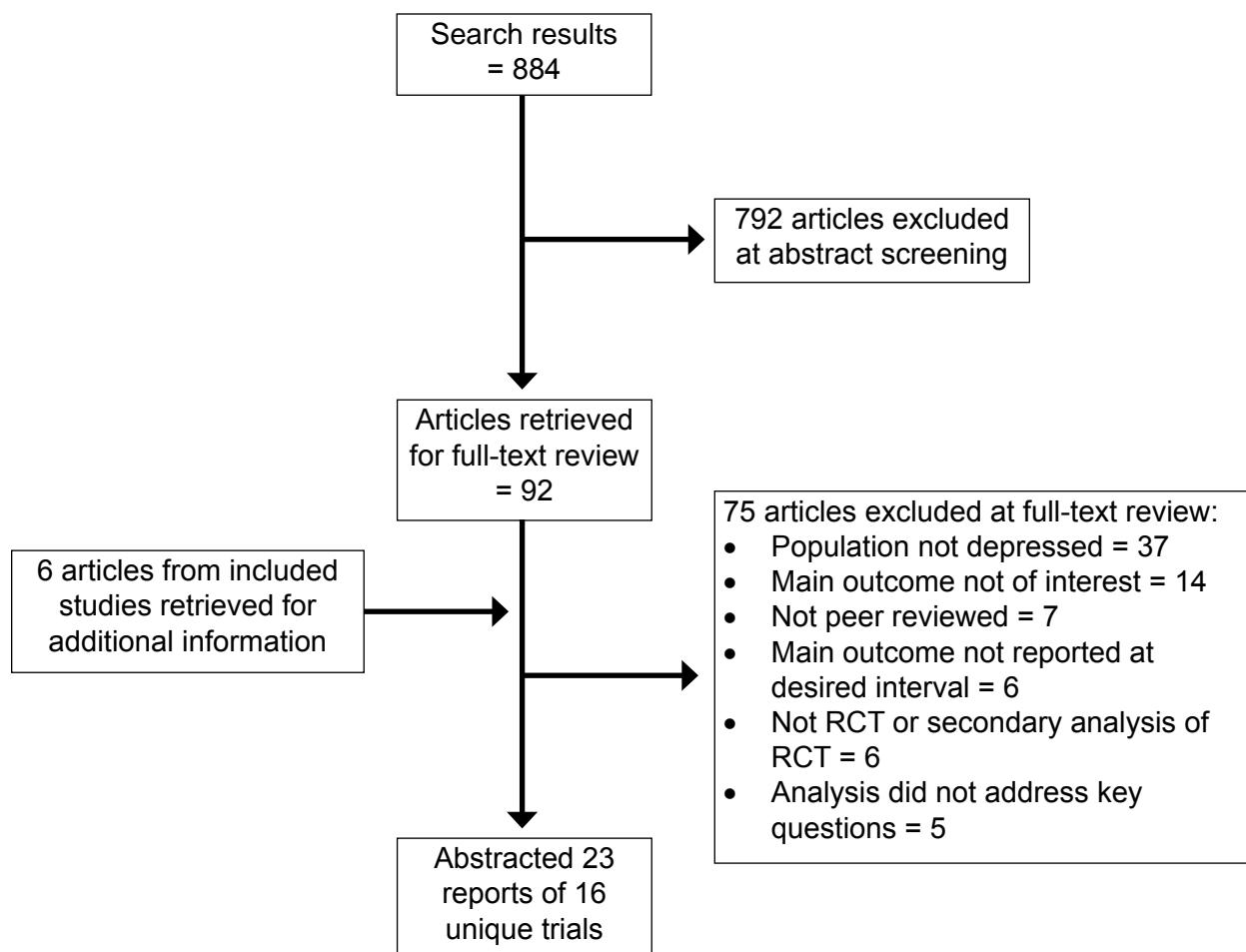


Table 3. Summary of Study Characteristics

Study, year	Study quality ^a	Sample size	Age Mean (SD)	% Female	% White	FTND Mean (SD)	Cigarettes per day Mean (SD)	Depressed mood at baseline Mean (SD)
Brown, 2001	Good	179 All MDD history positive	45.1 (9.3)	59.8	97.2	6.8 (1.9)	NR	BDI: 7.8 (6.31)
Covey, 1999	Fair	80 45% MDD history positive	33.8 ^b (8.2)	68.0 ^b	NR	NR	30.3 (10.1)	NR
Covey, 2002	Good	134 All MDD history positive	44.5 (10.7)	63.4	87.3	6.1(2.4) ^b	NR	BDI: 8.0 (7.7) CES-D: 14.9 (10.8) HDRS: 4.8 (4.4)
Duffy, 2006	Good	184 35% depressed smokers	57.0 (9.9)	16.0	90.0	NR	NR	NR
Evins, 2008	Good	199 All MDD history positive	43.0 (11.0)	49.0	NR	5.8 (2.2)	25.0 (11)	HDRS: 10.6 (6.3)
Hall, 1994	Fair	149 31% MDD history positive	40.6 (9.2)	52.0	88.0	6.4 (1.9)	24.9 (10.9)	BDI: 6.4 (5.9) ^c
Hall, 1996	Fair	201 22% MDD history positive	39.7 (NR)	52.0	92.0	NR	23.8 (9.8)	BDI: 6.7 (5.4)
Hall, 1998	Good	199 33% MDD history positive	41.9 ^c (9.9)	42.0 ^c	59.0 ^c	5.5 (2.2) ^c	21.8 (10.4) ^c	BDI: 12.1 (8.3) ^c
Hall, 2006	Good	322 All with current depression	41.5 ^b (12.4)	69.6	68.3	3.8 (2.4)	15.8 (10.0)	BDI: 20.6 (11.7) ^b
Hayford, 1999	Good	615 19% MDD history positive	42.2 – 43.7 ^d	54.6	96	FTQ: 7.1-7.3 (1.7) ^d	26.2(8.5) – 27.5(9.6) ^d	BDI: 4.1(4.2) – 4.7 (5.0) ^d
Kinnunen, 1996	Good	269 34% met criteria for depression	40.4 (12.6) 41.6 ^c (12.7)	51.0 61.0 ^c	82.0 80.0 ^c	5.6 (2.4) ^c	22 (10.4) ^c	NR
Kinnunen, 2008	Good	608 32% met criteria for depression	38.5 (11.3) ^c	51.0 ^c	78.6 ^c	Women: 5.6(2.3) ^c Men: 6.2 (2.3) ^c	Women: 21.0(10.0) ^c men:26.6(11.7) ^c	CES-D: Women: 24.8(7.0) ^c Men: 24.4 (6.9) ^c
MacPherson, 2010	Good	68 All with mildly elevated depressive symptoms	45.0 (12.2) ^b	48.5 (NR)	27.3	5.8 (1.8) ^b	18.8 (7.1) ^b	BDI: 10.8 (5.2) ^b
Munoz, 1997	Fair	136 78% MDE history positive	35.3 (NR)	38.2	0.0	NR	14.1 (8.2)	CES-D: 21.3 (13.9)
Saules, 2004	Fair	150 20% MDD history positive	39.8 (NR)	54.5	73.2	5.9 (NR)	NR	BDI: 4.92 (NR)
Vickers, 2009	Fair	60 All with current depression	41.8 (12.1) ^b	100.0	98.0 ^b	NR	21.6 (11.1) ^b	HRSD: 12.8 (6.0) CES-D: 29.8 (9.3)

^a Study quality assessed via key quality criteria described in AHRQ's General Methods Guide.

^b Mean for intervention arm only.

^c Mean for depressed subgroup.

^d Range of means from randomized groups at baseline.

Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies-Depression Scale, FTQ = Fagerstrom Tolerance Questionnaire, FTND = Fagerstrom Test for Nicotine Dependence, HDRS = Hamilton Depression Rating Scale, NR = not reported, MDD = major depressive disorder; MDE = major depressive episode

Most studies were of good quality according to quality criteria described in AHRQ's *General Methods Guide*.⁴² All studies were conducted in the U.S. with English-speaking participants except one, which was conducted with Spanish speakers living in the U.S.⁵¹ All reports, except one,⁵² reported smoking cessation outcomes for at least 6 months from the start of the trial. Most studies excluded participants with current MDD; however, 19 to 78% of participants in these studies had a history of MDD or exceeded a screening threshold for significant depressive symptoms. Of the studies that recruited smokers with depression, three recruited MDD history-positive participants,⁵³⁻⁵⁵ two recruited participants with current depression as measured by the CES-D⁵⁶ or the PRIME-MD,⁵⁷ and one recruited participants with mildly elevated depressive symptoms as assessed by the BDI-II.⁵⁸ For the remainder of this report, we refer to depression as (1) significant depressive symptoms as measured by validated assessment instrument (e.g., CES-D, BDI) or (2) a history of MDD.

KEY QUESTION 1. For patients with a history of a depressive disorder or current significant depressive symptoms, what is the comparative effectiveness of different smoking cessation strategies on smoking abstinence rates?

Intervention Types

All but two interventions tested combination therapies consisting of some type of counseling and pharmacotherapy.^{51,53} Of the studies that included behavioral counseling, the most common therapy was CBT conducted in person via small group or individual therapy. Only one included study conducted behavioral counseling via telephone.⁵⁹ Six studies included a behavioral mood management treatment.^{44,45,53,58-60} Mood management treatments ranged from smoking cessation-focused behavioral counseling augmented with one-time additional mood management counseling to intensive multisession group or individual CBT counseling. One study included mood management content delivered via mailed print materials.⁵¹ Of the studies that included antidepressant pharmacotherapies, four used bupropion,^{55,57,59,61} and three tested some other antidepressant (i.e., sertraline, fluoxetine, nortriptyline).^{45,54,62} Of studies that included antidepressants, two used NRT as a cotreatment,^{55,62} and two used NRT as a first-line therapy before offering bupropion.^{57,59} One study tested behavioral counseling plus a pill formulation of a long-acting opiate antagonist, naltrexone, as a smoking cessation aid.⁶³ No studies using varenicline were identified that met our eligibility criteria. Below, we summarize the evidence for smoking cessation interventions for adults with depression. When able, we conducted meta-analysis to quantitatively summarize evidence of comparative effectiveness of interventions.

Comparative Effectiveness of Smoking Cessation Strategies

NRT + Brief counseling versus placebo + brief counseling. Two studies of good quality compared the addition of nicotine gum to brief counseling compared to brief counseling plus placebo (Table 4).^{52,64} Kinnunen and colleagues (1996) compared the addition of 2 or 4 mg of nicotine gum to one-time brief counseling. Participants were advised to use the gum ad lib, with a target range of 9 to 15 pieces a day. In a subgroup analysis of participants with significant depressive symptoms as measured via the CES-D (n = 93), smokers with depression receiving either active gum dose were more likely to quit smoking than smokers with depression receiving

placebo gum (29.5% versus 12.5%; p-value NR) at 3 months post-quit date. In another trial, Kinnunen and colleagues (2008) reported the long-term effects of adding 2 or 4 mg of nicotine gum to 9 sessions of brief, 5- to 10-minute counseling sessions. Among participants with depression (n = 196), smokers receiving nicotine gum were more likely to remain abstinent at 12 month post-quit date than were smokers receiving placebo gum (15.1% versus 5.7%; p = 0.01).

Table 4. Smoking Cessation Studies of NRT Plus Brief Counseling Versus Placebo Plus Brief Counseling

Study, year	Intervention	Comparator	Follow-up duration
Kinnunen, 1996	Nicotine gum + one-time brief individual behavioral counseling	Placebo gum + one-time brief individual behavioral counseling	3 months
Kinnunen, 2008	Nicotine gum + 9 brief in-person individual counseling sessions	Placebo gum + 9 brief in-person individual counseling sessions	12 months

NRT + Behavioral counseling versus active control. Two studies compared the addition of NRT to behavioral counseling.^{44,57} In a two-by-two factorial design, Hall and colleagues (1996) compared nicotine gum to placebo gum with 10 sessions of group CBT smoking cessation counseling versus 10 sessions of health education (Table 5). Analyses were collapsed across treatment arms. Participants were given 2 mg nicotine gum or placebo gum starting at counseling session three and instructed to chew one piece per hour, 12 hours per day for the next 8 weeks. At Week 8, participants were given enough gum to taper treatment over the next 4 weeks. Smoking status was obtained and confirmed with biological assessments at Weeks 8, 12, 26, and 52. For MDD history-positive participants (n = 88), 22% receiving nicotine gum were abstinent compared to 33% receiving placebo gum at 52 weeks (p-value NR). This study was of fair quality due to omission of several key quality indicators (i.e., follow-up rates, randomization and allocation procedures, baseline characteristics).

In a study of good quality, Hall and colleagues (2006) offered nicotine patches plus 6 weeks of individual staged-care CBT behavioral counseling and computerized motivational feedback (Table 5). All participants had a current diagnosis of depression based on the PRIME-MD. Counseling sessions lasted 30 minutes and took place over 8 weeks. Participants were offered 21 mg patches for the first 6 weeks, 14 mg patches for the following 2 weeks, and then offered 7 mg patches for an additional 2 weeks. If patients did not quit smoking with NRT or relapsed during treatment, patients could request bupropion. A brief contact and smoking cessation referral served as the control condition. Smoking status was confirmed at 3, 6, 12, and 18 months postrandomization by expired carbon monoxide at ≤ 10 ppm. Staged-care counseling condition plus NRT outperformed brief contact control over time (OR = 4.55, 95% CI 1.04 to 19.93) with abstinence rates of 14.11% and 9.43% at 12 months and 18.4% and 13.21% at 18 months for the intervention and control, respectively.

Table 5. Smoking Cessation Studies of NRT Plus Behavioral Counseling Versus Active Control

Study, year	Intervention	Comparator	Follow-up duration
Hall, 1996 ^a	Nicotine gum + 10 sessions of group CBT smoking cessation counseling or 10 session health education	Placebo gum 10 sessions of group CBT smoking cessation counseling or 10 sessions health education	12 month
Hall, 2006	Transdermal nicotine patch (or bupropion if failed NRT) + staged motivational feedback + 6 sessions of individual CBT smoking cessation counseling	Brief contact + list of referrals to smoking cessation programs and stop smoking guide	18 months

^a Factorial design and analysis collapsed across treatment arms.

Synthesis of Evidence on NRT

Four studies addressed comparative effectiveness of adding single-form NRT (i.e., not combination NRT therapy) to other cotreatments versus an active control for adults with depression. Most trials reported smoking cessation outcomes of 12 months or greater from point of randomization. Of the four studies included in this review, only one intervened with adults with current depression;⁵⁷ results of other studies are from subgroup analyses. Cotreatments were heterogeneous and ranged from intensive CBT counseling to brief one-time counseling. However, most studies were of good quality and reported a small, positive effect for the use of NRT.

Antidepressant therapy + cotreatment versus placebo + cotreatment. Five trials reported results of adding antidepressants to cotreatments compared to active control condition for smokers with depression. Three of these studies, all of good quality and involving 255 smokers with depression, provided 6-month or greater outcomes data and were included in a meta-analysis.^{45,54,61} These studies compared antidepressants plus behavioral counseling to behavioral counseling plus placebo (Table 6). Two studies compared antidepressant therapy plus a cotreatment of behavioral counseling and NRT. These studies reported outcomes less than 6 months postrandomization and were not included in the meta-analysis.

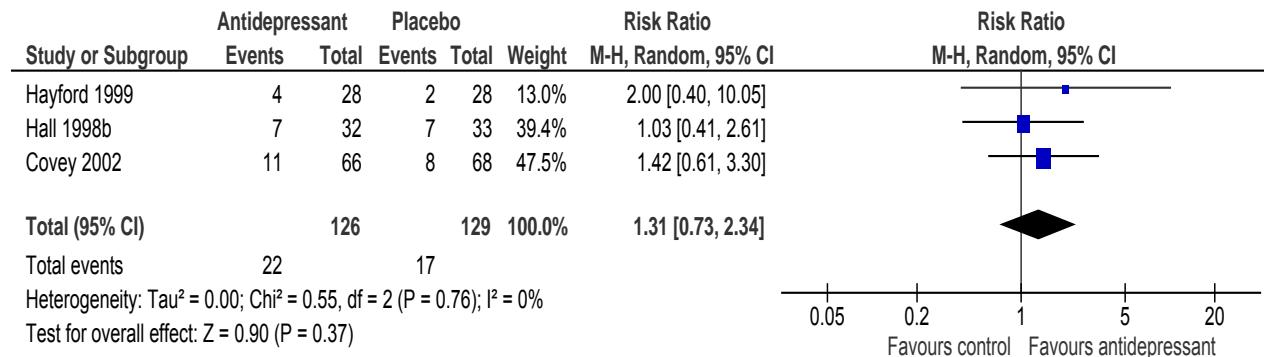
Table 6. Smoking Cessation Studies of Antidepressant Therapy Plus Behavioral Counseling Versus Placebo Plus Behavioral Counseling

Study, year	Intervention	Comparator	Follow-up duration
Covey, 2002	Sertraline + 9 individual in-person smoking cessation behavioral counseling sessions augmented with supportive approach to manage negative affect associated with quitting smoking	Placebo + 9 individual in-person smoking cessation behavioral counseling sessions augmented with supportive approach to manage negative affect associated with quitting smoking	34 weeks
Hall, 1998 ^a	Nortriptyline + 10 session of group CBT smoking cessation counseling or 10 session health education	Placebo + 10 session of group CBT smoking cessation counseling or 10 session health education	64 weeks
Hayford, 1999	Bupropion + 11 brief in-person individual counseling sessions	Placebo + 11 brief in-person individual counseling sessions	12 months

^a Factorial design and analysis collapsed across treatment arms.

Participants receiving antidepressants plus behavioral counseling were not more likely to be abstinent compared to participants receiving behavioral counseling plus placebo at 6-month postrandomization ($RR = 1.31$, 95% CI 0.73 to 2.34, Cochran Q = 0.55, $p = 0.76$, $I^2 = 0\%$) (Figure 3).

Figure 3. Risk of Smoking Cessation at Least 6 Months After Start of Antidepressant Therapy Plus Behavioral Counseling Compared With Placebo + Behavioral Counseling



In a study of good quality, Evins and colleagues (2008) tested the efficacy of adding 12 weeks of bupropion to a cotreatment consisting of 8 weeks of transdermal NRT and 13 sessions of group CBT smoking cessation counseling (Table 7).⁵⁵ All participants had a lifetime history of unipolar depressive disorder (UDD). Results were in the expected direction, favoring antidepressant use in combination with behavioral counseling plus NRT over behavioral counseling plus NRT alone (36% versus 31%; p-value NR). However, participants randomized to receive bupropion were no more likely to achieve smoking abstinence at end of treatment in intention-to-treat (ITT) analysis with dropouts considered smokers. Moreover, smoking abstinence was associated with depressive symptoms, regardless of antidepressant use.

Saules and colleagues (2004) also tested the addition of an antidepressant to a cotreatment of NRT and behavioral counseling (Table 7).⁶² This study was of fair quality. Participants in the intervention arm received 10 weeks of transdermal NRT plus 14 weeks of either 20 or 40 mg of fluoxetine in combination with 6 weeks of group CBT smoking cessation counseling. Again, results were in the expected direction and favored the addition of antidepressant therapy. However, among participants who were history positive for MDD ($n = 30$), Saules found no significant differences in abstinence rates when fluoxetine was added to NRT and intensive behavioral counseling.

Table 7. Smoking Cessation Studies of Antidepressant Therapy Plus Behavioral Counseling Plus NRT Versus Placebo Plus Behavioral Counseling Plus NRT

Study, year	Intervention	Comparator	Follow-up duration
Evins, 2008	Bupropion + 13 group CBT smoking cessation counseling + NRT patch	Placebo + 13 group CBT smoking cessation counseling + NRT patch	13 weeks
Saules, 2004	Fluoxetine + 6 group CBT smoking cessation counseling + NRT patch	Placebo + 6 group CBT smoking cessation counseling + NRT patch	12 months

Synthesis of Evidence on Antidepressants

Five studies addressed comparative effectiveness of adding antidepressants to other cotreatments versus an active control (e.g., counseling + NRT + placebo) for adults with depression. For included studies, antidepressants were prescribed at therapeutic doses. Only two included studies recruited participants with histories of MDD;^{54,55} results of other studies are from subgroup analyses. All cotreatments included multisession counseling, and four studies were of good quality. However, there was heterogeneity in antidepressant type across included studies. Only one used bupropion, the only antidepressant with an FDA indication for smoking cessation. Overall, we did not find enough evidence to support adding antidepressants to other smoking cessation cotreatments in order to improve smoking cessation rates among persons with depression.

Mood management treatment + cotreatment versus cotreatment/active control. Six trials reported results of adding mood management treatments to behavioral counseling (Table 8). Other cotreatments given to all participants include NRT,^{44,58-60} nortriptyline,⁴⁵ or NRT plus bupropion or paroxetine.⁵⁹ Five of these studies, involving 402 smokers with depression, provided sufficient data for meta-analysis.^{44,45,53,58,60}

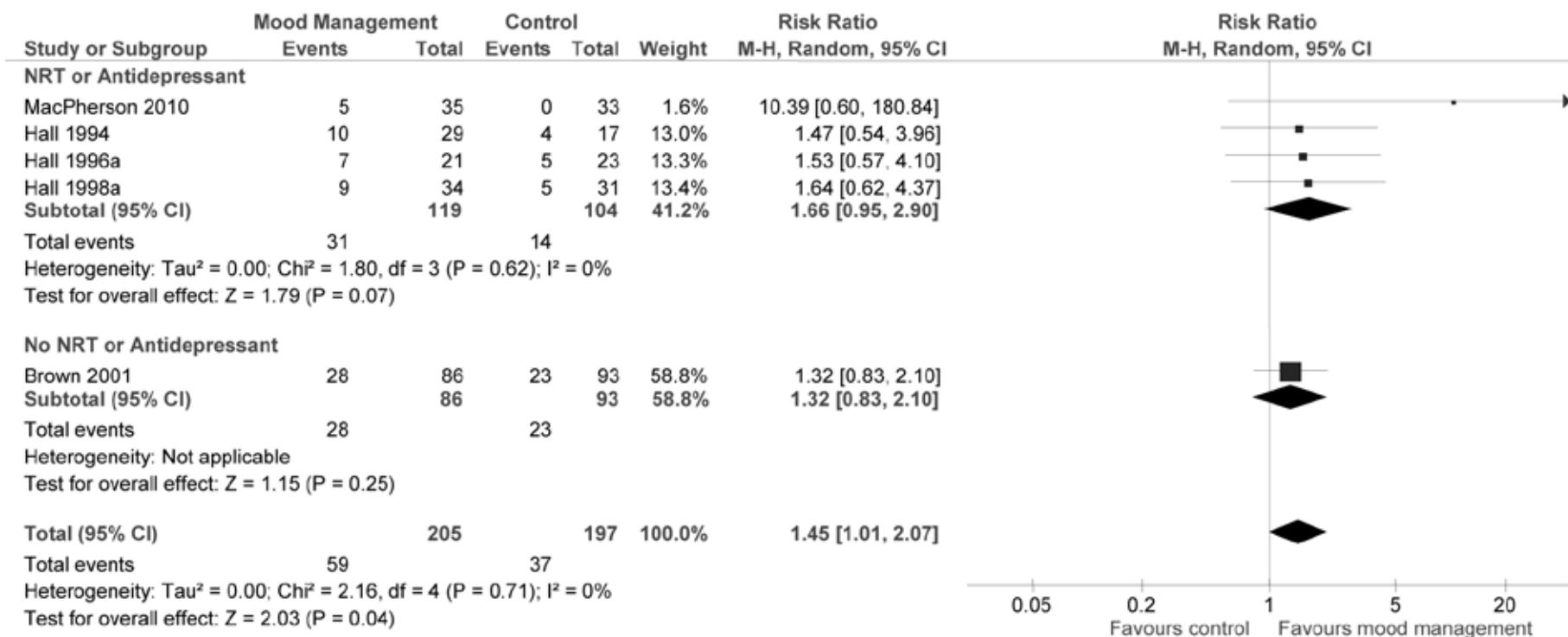
Table 8. Smoking Cessation Studies With a Mood Management Treatment Component

Study, year	Intervention	Comparator	Follow-up duration
Mood management treatment + behavioral counseling versus behavioral counseling			
Brown, 2001	8 group sessions of depression and smoking cessation CBT	8 group sessions of smoking cessation CBT	12 months
Mood management treatment + behavioral counseling + NRT versus behavioral counseling + NRT			
Hall, 1994	5 group sessions of CBT mood management + 5 group sessions of smoking cessation counseling + nicotine gum	5 group sessions of smoking cessation counseling + nicotine gum	52 weeks
Hall, 1996 ^a	5 group sessions of CBT mood management + 5 group sessions of smoking cessation counseling + nicotine gum	10 sessions of standard group smoking cessation health education + nicotine gum	52 weeks
MacPherson, 2010	8 group sessions of smoking cessation CBT that included behavioral activation therapy + NRT patch	8 group sessions of smoking cessation CBT + NRT patch	26 weeks
Mood management treatment + behavioral counseling + NRT/antidepressant versus control			
Duffy, 2006	9 to 11 sessions of combined smoking, depression, alcohol abuse telephone CBT + bupropion + NRT (if failed bupropion monotherapy in the past) OR NRT + paroxetine (if failed bupropion in the past for depression)	One-time behavioral counseling and referral to appropriate services for substance use/abuse and/or depression	6 months
Hall, 1998 ^a	5 group sessions of CBT mood management + 5 group sessions of smoking cessation counseling + nortriptyline or placebo	10 session health education + nortriptyline or placebo	64 weeks

^aFactorial design and analysis collapsed across treatment arms.

All studies included in the meta-analysis were in the expected direction, favoring the addition of mood management treatment to smoking cessation cotreatments ($RR = 1.45$, 95% CI 1.01 to 2.07, Cochran Q = 2.16, $p = 0.71$, $I^2 = 0\%$). Subgroup analysis suggests smoking cessation may be more likely when mood management treatment was added to cotreatments that included NRT or antidepressants in addition to behavioral counseling ($RR = 1.66$, 95% CI 0.95 to 2.90, Cochran Q = 1.8, $p = 0.62$, $I^2 = 0\%$) (Figure 4). However, confidence intervals overlap, and this contrast was not statistically significant.

Figure 4. Risk of Smoking Cessation at Least 6 Months After Start of Mood Management Treatment Plus Cotreatment Compared to Active Control



In a study of good quality, Duffy and colleagues (2006) tested a combined smoking, depression, and alcohol abuse CBT counseling protocol for head-and-neck cancer survivors.⁵⁹ Smokers who were depressed were offered NRT and bupropion or paroxetine. Content was delivered by telephone over the course of 9 to 11 counseling sessions. One-time behavioral counseling and referral to appropriate follow-up services served as the comparator condition. Among participants who were smokers and depressed at baseline (n = 64), 51% were nonsmokers at 6 months from end of treatment compared to 17% in the control arm (p-value NR). Smoking status was verified by self-report only.

Synthesis of Evidence on Mood Management Treatment

Six trials addressed comparative effectiveness of adding mood management treatments to other smoking cessation cotreatments versus an active control for adults with depression. All trials reported smoking cessation outcomes at 6 months or greater from point of randomization. Four of these trials were of good quality. Of the five trials included in the meta-analysis, only two studies recruited participants with either a history of MDD⁵³ or elevated depressive symptoms.⁵⁸ Results of other studies are from subgroup analyses. Overall, results indicate a small, positive effect for the addition of mood management treatment to smoking cessation cotreatments.

Other intervention strategies. Three additional trials tested other types of interventions. These are summarized below and in Table 9.

In a study of fair quality, Covey and colleagues (1999) tested behavioral counseling plus a long-acting opiate antagonist, naltrexone, as a smoking cessation aid.⁶³ Participants received six individual brief behavioral counseling sessions. Participants in the control arm received the same counseling plus placebo. Smoking status was verified by blood cotinine level of < 15 ng/ml. Of the 36 participants with a history of MDD, results favored use of naltrexone in combination with counseling over counseling plus placebo (28.6% versus 9.1%; p-value NR).

Munoz and colleagues (1997) tested the efficacy of a self-administered mood management intervention plus smoking cessation guide compared to a smoking cessation guide alone delivered through the mail for Spanish-speaking smokers.⁵¹ To be eligible for the trial, participants needed to indicate that they were either “completely” or “very” sure they wanted to quit smoking in the next 3 months. The smoking cessation guide was a 36-page booklet from the National Cancer Institute and contained tips on how to quit smoking. The mood management treatment consisted of relaxation exercises, self-monitoring booklet, and pleasant activity guide. An audio cassette explained how to use the materials. Among participants with a history of MDE, the addition of mailed mood management content improved cessation rates over the mailed smoking cessation guide (38.5% versus 7.4%; p = 0.01) at 6 months postrandomization. For smokers with current MDE, no significant differences were found (17.9% versus 8.0%; p = 0.15). This study was of fair quality.

In another fair study, Vickers and colleagues (2009) conducted a small randomized pilot to test the feasibility of behavioral counseling to promote exercise as a smoking cessation intervention for depressed female smokers.⁵⁶ Women were randomized to receive brief smoking cessation counseling plus 6 weeks of transdermal NRT, plus either 10 weeks of CBT to encourage exercise or a health education contact control condition. The intervention was feasible but did not significantly improve smoking cessation rates compared to the health education control (17% versus 23%; p = 0.75).

Table 9. Other Smoking Cessation Intervention Strategies Studies

Study, year	Intervention	Comparison	Follow-up duration
Covey, 1999	Naltrexone + 6 individual in-person behavioral counseling sessions	Placebo + 6 individual in-person behavioral counseling sessions	6 months
Munoz, 1997	Mailed smoking cessation guide + mood management guide	Mailed smoking cessation guide + mood management guide at 3 months delayed	6 months
Vickers, 2009	10 in-person individual exercise counseling sessions that include brief smoking cessation counseling + NRT	10 in-person individual health education sessions that include brief smoking cessation counseling + NRT	24 weeks

Synthesis of Evidence on Other Intervention Strategies

We identified three other types of smoking cessation strategies, each with only one RCT. Covey and colleagues (1999) and Munoz both reported positive results for participants with depression. However, studies were of fair quality (e.g., no ITT analysis, lack of detail on study measures, randomization and allocation concealment procedures not well described) and with select populations (e.g., Spanish speakers), which limits confidence in the estimates of effects and applicability of results to other populations. Results of Vickers and colleagues (2009) demonstrated no effect for using exercise counseling as a smoking cessation intervention strategy for smokers with depression.

KEY QUESTION 2. For patients with a history of a depressive disorder or current significant depressive symptoms, are there differential effects of smoking cessation strategies by depression status (i.e., history of MDD, current depressive symptoms, current MDD)?

Only two studies provided sufficient information to report differential effectiveness of smoking cessation intervention strategies by depression status. For both reports, study researchers conducted subgroup analysis only; no treatment by depression interaction effects were directly tested.

Evins and colleagues (2008) recruited 199 smokers who had a lifetime diagnosis of UDD. Participants were randomized to 12 weeks of bupropion versus placebo. Both groups received a cotreatment consisting of 8 weeks of transdermal NRT and 13 sessions of group CBT smoking cessation counseling.⁵⁵ Among participants who were history positive for unipolar depression ($n = 109$), 39% in the bupropion arm and 32% in the control arm were abstinent at the end of trial (p-value NS). Among participants with current depression ($n = 90$), bupropion did not significantly improve smoking cessation rates compared to cotreatment control condition (33% versus 31%; p-value NS).

Munoz and colleagues (1997) tested the efficacy of a mailed self-administered mood management intervention plus smoking cessation guide compared to only a smoking cessation guide for Spanish-speaking smokers.⁵¹ The addition of mailed mood management content improved cessation rates over the mailed smoking cessation guide (38.5% versus 7.4%; $p = 0.01$) at 6 months postrandomization for participants with a history of MDE. Smokers with current MDE did not experience significant differences (17.9% versus 8.0%; $p = 0.15$).

KEY QUESTION 3. For patients with a history of a depressive disorder or current significant depressive symptoms, are there differential effects of smoking cessation strategies by gender?

Only one included study reported a significant treatment by gender interaction among study participants with a history of or current depression.⁶³ Covey and colleagues (1999) found a significant treatment by gender by depression interaction. Women with past histories of MDD (n = 26) experienced higher quit rates when randomized to receive naltrexone in combination with six sessions of individual behavioral counseling compared to women with depression receiving placebo control at 6 months (22.2% versus 0%; p = 0.04). Men with past histories of MDD (n = 10) did not experience significantly higher quit rates with naltrexone at 6 months.

KEY QUESTION 4: For patients with a history of a depressive disorder or current significant depressive symptoms, does treatment effectiveness differ by whether smoking cessation/depression treatments are delivered concurrently or sequentially?

No studies directly compared smoking cessation and depression treatments delivered concurrently versus sequentially.

KEY QUESTION 5: What is the nature and frequency of adverse effects of smoking cessation treatments in patients with a history of a depressive disorder or current significant depressive symptoms?

Table 10 details reported adverse effects of the 16 included trials. Overall, 11 studies did not provide information on the nature and frequency of adverse effects of treatments. Of the five studies that reported adverse effects, three provided some level of detail about the magnitude and significance of adverse effects; other studies reported too few cases to conduct statistical tests. These three studies all evaluated the addition of antidepressants with other smoking cessation treatments. In two of the three studies, selected adverse effects were more common in patients randomized to antidepressants.

Table 10 also summarizes change in depressive symptoms from baseline to follow-up when comparing intervention and control arms among participants classified as depressed at baseline. Seven trials did not report changes in depressive symptoms from baseline to follow-up per arm for participants classified as depressed at study entry. Six studies reported no significant differences. Of three studies that reported significant differences, only Vickers and colleagues (2009) reported more favorable changes in depressive symptoms associated with the control arm compared to the intervention arm. Kinnunen and colleagues (1996) and MacPherson and colleagues (2010) reported more favorable changes in depressive symptoms associated with the intervention arms.

Table 10. Adverse Effects of Included Studies

Study, year	Intervention	Adverse effects reported^a (% reported in intervention versus control)	Change in depressive symptoms^b
Brown, 2001	8 group sessions of depression and smoking cessation CBT	NR	No difference between intervention and control arms
Covey, 1999	Naltrexone + 6 individual in-person behavioral counseling sessions	Panic attack, malaise, sleeplessness, concentration difficulty, nausea and vomiting, disoriented and shaky, spaciness, dizzy, abdominal pain, lightheadedness, shortness of breath	NR
Covey, 2002	Sertraline + 9 individual in-person smoking cessation behavioral counseling sessions augmented with supportive approach to manage negative affect associated with quitting smoking	NR	No difference between intervention and control arms
Duffy, 2006	9 to 11 sessions of combined smoking, depression, alcohol abuse telephone CBT + bupropion + NRT (if failed bupropion monotherapy in the past) OR NRT + paroxetine (if failed bupropion in the past for depression)	NR	No difference between intervention and control arms
Evins, 2008	Bupropion + 13 group sessions of CBT smoking cessation counseling + NRT patch	NR	No difference between intervention and control arms
Hall, 1994	5 group sessions of CBT mood management + 5 group sessions of smoking cessation counseling + nicotine gum	NR	NR
Hall, 1996	5 group sessions of CBT mood management + 5 group sessions of smoking cessation counseling + nicotine gum	NR	No difference between intervention and control arms
Hall, 1998	5 group sessions of CBT mood management + 5 group sessions of smoking cessation counseling + nortriptyline	Dry mouth (78% vs 33%) ^c , lightheadedness (49% vs 22%) ^c , shaky hands (23% vs 11%) ^c , blurry vision (16% vs 6%) ^c	NR
Hall, 2006	Transdermal nicotine patch (or bupropion if failed NRT) + staged motivational feedback + 6 sessions of individual CBT smoking cessation counseling	NR	No difference between intervention and control arms
Hayford, 1999	Bupropion + 11 brief in-person individual counseling sessions	Headache (29% vs 31-33%) , insomnia (21% vs 30-35%) ^c , rhinitis (17% vs 10 to 12%), dry mouth (5% vs 13%) ^c , increased anxiety (11% vs 5-7%)	NR
Kinnunen, 1996	Nicotine gum + one-time brief individual behavioral counseling	NR	Decrease in NRT gum arm and no change in placebo arm

Study, year	Intervention	Adverse effects reported^a (% reported in intervention versus control)	Change in depressive symptoms^b
Kinnunen, 2008	Nicotine gum + 9 brief in-person individual counseling sessions	Heart palpitations, nausea, vomiting, dizziness, breathing difficulties, tongue blisters, damage to dental work, sore jaw ^d	NR
MacPherson, 2010	8 group sessions of smoking cessation CBT that included behavioral activation therapy + NRT patch	NR	Greater decrease in intervention arm compared to control arm
Munoz, 1997	Mailed smoking cessation guide + mood management guide	NR	NR
Saules, 2004	Fluoxetine + 6 group sessions of CBT smoking cessation counseling + NRT patch	Adverse effects not more common in intervention arms but did not list types	NR
Vickers, 2009	10 in-person individual exercise counseling sessions that include brief smoking cessation counseling + NRT	NR	Decrease in health education arm and increase in exercise counseling arm

^a Adverse effects reported for all subjects in trial.

^b For participants within depressed subgroup, statistically significant change in depressive symptoms from baseline to follow-up.

^c Statistically significant and greater proportion affected in intervention arm compared to proportion affected in control arm.

^d Less than 2% of low-nicotine dependent and 6% of high-nicotine dependent participants in the intervention arms experienced most common NRT gum adverse effects (i.e., heart palpitations, nausea, dizziness).

Abbreviations: CBT = cognitive behavioral therapy, NR = not reported, NRT = nicotine replacement therapy

DISCUSSION

SUMMARY AND DISCUSSION

There is a synergistic and potentially bidirectional relationship between depression and smoking.^{6,14,19,65,66} Smokers with depression are significantly less likely to quit smoking, and depressed individuals are more likely to be smokers.⁵⁻⁷ Consequently, there is a need to identify effective smoking cessation interventions for this disproportionately affected population. We conducted a systematic review of smoking cessation intervention strategies for persons with depression. We also sought to examine differential effects of smoking cessation treatment by depression status, gender, and treatment sequencing and to characterize adverse effects of smoking cessation treatments in patients with depression. We found insufficient evidence to examine moderator effects and to characterize adverse effects. However, findings suggest several promising smoking cessation strategies for persons with depression. We summarize and discuss our findings here.

We identified three types of intervention strategies: cotreatments augmented with behavioral mood management treatment (six trials), cotreatments augmented with antidepressant therapy (five trials), and cotreatments augmented with NRT (four trials). Cotreatments generally consisted of some type of smoking cessation counseling (e.g., brief, behavioral), with or without NRT. We also identified three additional trials that used behavioral counseling to promote exercise plus NRT,⁶⁷ mailed self-help materials,⁵¹ or long-acting opiate antagonists plus behavioral counseling⁶³ as smoking cessation interventions. Overall, we found insufficient evidence to support exercise behavioral counseling, mailed self-help materials, or naltrexone as smoking cessation strategies for smokers with depression. Although both naltrexone and mailed self-help materials showed positive effects in single trials, further study is required to assess the efficacy of these strategies. Also, it is possible that we may have missed studies with unpublished but relevant data.

We did not identify any studies using varenicline that met our eligibility criteria. Varenicline stimulates dopamine release, which reduces nicotine cravings and withdrawal symptoms, and blocks nicotine receptors, which may reduce the pleasurable effects of continued nicotine usage. Pooled results of two RCTs showed significantly higher abstinence rates at the end of 12 weeks of varenicline treatment compared to both placebo and bupropion.^{68,69} However, given the latest concerns about mental health instability within the veteran population,⁷⁰ varenicline should be reserved for special cases and will require close observation.

Smokers with depression are more likely to have increased levels of negative mood both precessation and postcessation.^{15,71-73} Also, negative mood is associated with greater relapse rates.^{74,75} Mood management therapy may serve to moderate negative mood associated with making and maintaining a quit attempt.⁷⁴ Therefore, smokers with depression may respond better to smoking cessation interventions augmented with mood management techniques. Our results support this hypothesis. Pooled results from our meta-analysis demonstrate a small, positive effect of adding behavioral mood management therapy to smoking cessation cotreatments. The number needed to treat with mood management therapy plus NRT or antidepressants is 12 persons to get 1 additional person to quit smoking for at least 6 months. The strength of evidence is moderate. Only six identified trials provided enough detail to assess cessation rates among

smokers with depression. Moreover, we found significant heterogeneity in intensity of mood management therapy across studies, which may influence estimates of effectiveness.

All of the included antidepressant trials showed small, positive effects on smoking cessation, but a summary estimate of effect was not statistically significant. However, the strength of evidence for the lack of benefit for antidepressants as a smoking cessation aid for smokers with depression is low. Sample sizes were small and the number achieving cessation few, which limits precision of estimates of effects and our ability to detect statistically significant differences. Also, we were able to include only five trials, of which there was significant heterogeneity in antidepressant type. Only bupropion and nortriptyline have proven efficacy as smoking cessation pharmacotherapies.^{36,76} Meta-analysis results show little smoking cessation benefit for selective serotonin reuptake inhibitors such as sertraline and fluoxetine in the general population of smokers.³⁶ Because results may differ by pharmacotherapy used, caution should be taken in applying our findings to other antidepressants that may be used to aid smokers with depression in quitting smoking.

Offering NRT to smokers with depression appears to have a small, positive effect on smoking cessation rates among depressed smokers. Cessation rates ranged from 14 to 22% in the three included studies that reported outcomes of 12 months or longer.^{44,57,64} These cessation rates are higher than the 3 to 5% of smokers who successfully maintain quit attempts a year later without treatment aids⁷⁷ and are comparable to NRT quit rates in the general population of smokers.³⁵ Yet, long-term cessation rates were lower for patients with current depressive symptoms⁵⁷ than for those who are history positive for MDD⁴⁴ (14% versus 22%, respectively). Smokers with current depressive symptoms may have greater difficulty quitting due to more issues with nicotine withdrawal or worsening of depressive symptoms during a quit attempt.⁷⁸ Smokers with current depressive symptoms may need additional support to make and maintain a quit attempt. The strength of evidence for NRT use among smokers with depression is moderate. Data were sparse; we were able to include only four trials. However, studies were of good quality and reported consistent results.

STRENGTHS AND LIMITATIONS

Our systematic review has a number of strengths that are consistent with the QUORUM reporting statement and the AMSTAR quality assessment of systematic reviews. These include a protocol-driven approach, a comprehensive literature search of multiple electronic databases, double data abstraction, quality assessment of the primary studies, and appropriate methods for combining estimates of effect. Despite these strengths, our review has several limitations.

Foremost is that few RCTs exist that test smoking cessation interventions among smokers with depression. The paucity of literature has important implications for this evidence review. First, in order to make meaningful comparisons, we created broad intervention categories that used different types of counseling modes (e.g., group, individual) and pharmacotherapies. Within each category, there is considerable heterogeneity. For example, we identified few medication trials and fewer with the same type of medication. Ideally, we would have wanted to analyze trials by specific medications since treatment effects may vary within broad classes of medications.

Second, few trials recruited smokers with current depression. In fact, many trials excluded patients with current or recent histories of depression. Therefore, many reports based

classifications of depression on self-reported screening criteria (e.g., CES-D, BDI) for significant depressive symptoms. Self-report scales may be measures of general emotional distress or negative affect rather than specific depressive symptoms. In primary care settings, a positive depression screen has a positive predictive value of $\leq 50\%$ for MDD.⁷⁹ Thus, our review contains heterogeneity among the group of subjects included in trials classified as depressed. To address this heterogeneity, our protocol specified a stratified analysis by type of depression (e.g., history of MDD, current depressive symptoms, current MDD), but there were too few trials in any intervention category to follow this planned approach. Also, time since last episode, chronicity of depression, and other important variations in depressive disorders may be associated with outcomes. For example, some evidence supports that those with recurrent MDD compared to a single episode have worse outcomes⁶ and may differentially respond to certain interventions that target their depressive symptoms during a quit attempt. Our review is unable to address this issue. Moreover, most studies included in this report excluded participants with comorbid alcohol or substance abuse. Results are likely not generalizable to groups with these comorbidities.

In many instances, we examined subgroup data for this evidence review. Including studies that reported on subgroups of individuals with depression has limitations. By doing so, we introduce the possibility of false-negative studies because many of these studies were not powered to detect clinically important treatment effects in depressed subgroups. Meta-analysis helps to address this limitation, but with relatively few studies of small sample sizes, our analyses may remain underpowered. In addition, subgroup analyses, unless specified a priori and part of a limited number of subgroups evaluated, may produce false-positive or spurious results.⁸⁰

Data were limited on the majority of our key questions. No studies tested differential effects of smoking cessation interventions by treatment sequencing among smokers with depression. Literature on treatment differences by gender and depression status was also sparse. Our results on adverse effects are limited as well. Ideally, we would have conducted a separate search for adverse effects in the observational literature. However, it is unlikely that much literature exists on these types of interventions specific to our population of interest—smokers with a history of depression or with current depression. Lastly, few of the trials in this evidence review included VA users. Although veterans have higher rates of depression and smoking compared to the general population,⁸⁻¹² results should be generalizable to the VA population.

CONCLUSIONS

We identified only 16 trials, encompassing 1756 smokers with depression. Just three of these trials actively recruited participants with elevated depressive symptoms.^{57,58,67} Most patients included in this review were history positive for depression; findings best apply to this population. For patients with current depression, we have little data. We were able to conduct meta-analyses of only two contrasts: (1) addition of any type of antidepressant and (2) treatment augmented by behavioral mood management counseling. Results of this systematic review indicate promising smoking cessation strategies for smokers with depression.

Table 11 summarizes the strength of evidence for each of our key questions and contrasts. Our results support a small, positive effect for adding mood management counseling for smoking cessation among patients with depression. However, it is uncertain if the effects of mood management counseling may differ by therapy mode (individual versus group therapy). We did not

find adequate support for adding antidepressants; we may be underpowered to detect statistically significant differences. Evidence suggests support for adding NRT; however, included trials were too varied to be analyzed quantitatively. While most trials included in this evidence review were of good quality and had consistent results, data were sparse. We expect that future research will likely have an important impact on our confidence in the estimates of effectiveness of smoking cessation treatments for smokers with depression. However, evidence suggests that depression does not need to be resolved before tobacco cessation treatment is initiated. Smokers with depression can successfully maintain smoking cessation. To improve the likelihood of success, health care providers should consider encouraging their depressed patients who smoke to seek smoking cessation services that include behavioral mood management treatment and NRT.

Table 11. Summary of the Strength of Evidence for Key Questions 1 to 5

Number of studies (subjects)^a	Domains pertaining to strength of evidence				Magnitude of effect and strength of evidence
	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	
Key Question 1: NRT					Moderate SOE
Moderate SOE 4 (699)	RCT/ Good	Consistent	Direct	Imprecise	14 to 22%
Key Question 1: Antidepressant therapy					Low SOE
5 (484)	RCT/Good	Consistent	Direct	Imprecise	1.48 (95% CI 0.86 to 2.54) ^b
Key Question 1: Mood management treatment					Moderate SOE
6 (466)	RCT/Good	Consistent	Direct	Imprecise	1.45 (95% CI 1.01 to 2.07) ^c
Key Question 1: Other intervention strategies					Low SOE
3 (202)	RCT/ Fair	Inconsistent	Direct	Imprecise	17 to 39%
Key Question 2: Differential effects by depression status					Insufficient SOE
2 (305)	RCT/ Good	Inconsistent	Direct	Imprecise	18 to 39%
Key Question 3: Differential effects by gender					Insufficient SOE
1 (36)	RCT/ Good	Consistent	Direct	Imprecise	22%
Key Question 4: Differential effects by treatments delivered concurrently or sequentially					Insufficient SOE
0 (0)	---	---	---	---	---
Key Question 5: Adverse effects					Insufficient SOE
5 (1,652)	RCT/ Good	Inconsistent	Indirect	Imprecise	

^a Numbers reflect participants with depression only for KQs 1 to 4 and all study participants for KQ 5.

^b Magnitude of effect calculated from 3 trials included in meta-analysis (n = 255).

^c Magnitude of effect calculated from 5 trials included in meta-analysis (n = 402).

Abbreviations: CI = confidence interval, RCT = randomized controlled trial, SOE = strength of evidence

FUTURE RESEARCH

While this review provides some evidence about smoking cessation strategies for patients with depression, more work is needed in this area. First, we found very little trial data on intervening with smokers who are currently depressed. Persons with depression are about twice as likely to be smokers than persons without depression.⁵ Moreover, smokers with depression may experience more challenges when trying to make and maintain a quit attempt, such as greater negative mood symptoms from withdrawal, higher nicotine dependence, and greater likelihood of relapse, than smokers without depression.^{17,18,21,22,24,81} Secondary analysis of existing smoking cessation trial data could advance our understanding of smoking cessation strategies for patients with depression. Future studies should be designed to test smoking cessation interventions for this vulnerable population. Next, within the trials we identified, we found little research on key moderators that may influence treatment effectiveness (e.g., gender, depression status). Moderator analysis will facilitate subgroup identification, which may lead to better treatment matching.⁶

Evidence is growing that combination pharmacotherapy is effective for the general population of smokers.⁸² In 2009, the VA Pharmacy Benefits Management (PBM) Services released recommendations for the use of combination pharmacotherapy for tobacco use cessation. The VA PBM recommends combination NRT that involves the use of a longer acting NRT such as the patch in conjunction with a short-acting NRT (e.g., gum, inhaler, nasal spray) (<http://www.pbm.va.gov>). Future studies should be designed to allow for direct comparisons between combinations of likely efficacious NRT therapies for smokers with depression. Also, it is not known how to combine depression and smoking pharmacotherapies. Take, for example, a patient with depression who is improving on sertraline but wants to stop smoking. Should the provider add bupropion or change from sertraline to bupropion, which may risk worsening of depression? Future trials should investigate combination smoking cessation and depression pharmacotherapy among smokers with depression.

Behavioral counseling plus pharmacotherapy is considered the gold standard of care for effective smoking cessation interventions.^{29,37,39} Smokers with psychiatric comorbidities may benefit from combined behavioral counseling and pharmacotherapy with longer therapeutic approaches (i.e., exceeding 8 to 12 weeks) to reduce likelihood of dropout and depression relapse.⁴¹ Thus, future research should be designed to optimize dose, duration, and frequency of both behavioral counseling and pharmacotherapies. In addition, it is likely that patients with depression need strategies that target both depressive symptoms and smoking. Future research should seek to answer questions about the optimal sequencing of depression and smoking treatment content of smoking cessation interventions. Moreover, we were unable to tease apart the active components of individual therapies. Thus, important issues, such as mode of therapy (e.g., individual, group, telephone) and key therapeutic components (e.g., goal setting, monitoring of thoughts and moods, social support), cannot be answered by this systematic review. Future studies should be designed to disentangle active ingredients of behavioral counseling and the effects of delivery channels. Beyond scanning the reports included in this review, no attempt was made to synthesize information about adverse effects from observational studies and other data sources. Future research should be conducted to characterize adverse effects of treatment, including changes in negative affect and depressive symptoms.

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