



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

**EXECUTIVE SUMMARY**

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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](mailto:nicole.floyd@va.gov).

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## EXECUTIVE SUMMARY

### BACKGROUND

Smoking is disproportionately higher among persons with depression (45% versus 22%). Furthermore, 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. Despite the complex relationship between tobacco use and depression, smokers with depression are motivated to quit smoking and should be offered cessation services. Several evidence-based smoking cessation treatments are effective for the general population of smokers. Yet the comparative effectiveness of these strategies in smokers with depression is uncertain. Also, it is uncertain if factors that may facilitate targeted interventions, such as depression status, gender, and treatment sequencing (i.e., concurrent versus sequential) for mood and smoking cessation, differentially impact the effectiveness of smoking cessation interventions. We conducted a systematic review of the peer-reviewed literature to answer the following key questions:

**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?

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.

## METHODS

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. Titles, abstracts, and articles were reviewed in duplicate by trained researchers. A trained researcher abstracted data from published reports into evidence tables; a second reviewer overread the evidence tables. When study designs and outcomes reported were similar, we estimated pooled risk ratios (RR) with 95% confidence intervals (CI) 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. All other data were narratively summarized.

## RESULTS

We screened 884 titles, rejected 792, and performed full-text reviews on 92 articles. We manually 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. The 23 included reports encompassed 16 unique trials, of which only three recruited participants with current depression.

**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?

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 exercise behavioral counseling plus NRT, mailed self-help materials, or long-acting opiate antagonist plus behavioral counseling as smoking cessation interventions.

Pooled results from our meta-analysis demonstrate a small, positive effect of adding behavioral mood management treatments to smoking cessation cotreatments (RR = 1.45, 95% CI 1.01 to 2.07). All of the included antidepressant trials showed small, positive effects when comparing antidepressants plus behavioral counseling to placebo plus behavioral counseling, but a summary estimate of effect from meta-analysis was not statistically significant (RR = 1.31, 95% CI 0.73 to 2.34). We were unable to conduct a meta-analysis of NRT trials. Three of the four NRT trials showed positive effects with clinically significant abstinence. Two of these NRT trials reported statistically significant differences. Results from three of the four included studies suggest that offering NRT appears to have a small, positive effect on smoking cessation rates among smokers who are depressed. We found insufficient evidence to support exercise behavioral counseling, mailed self-help materials, or naltrexone, although both naltrexone and mailed self-help materials showed positive effects in single trials.

**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 information on differential effectiveness of smoking cessation intervention strategies by depression status. Study researchers conducted subgroup analysis only; no treatment by depression interaction effects were directly tested. Among participants who were history positive for unipolar depression in Evins (2008), 39% in the bupropion plus behavioral counseling plus NRT arm and 32% in the placebo plus behavioral counseling plus NRT control arm were abstinent at the end of trial (p-value NS). Bupropion did not significantly improve smoking cessation rates compared to active control condition for participants with current depression (33% versus 31%; p-value NS). In Munoz and colleagues (1997), the addition of mailed mood management content improved cessation rates over a mailed smoking cessation guide (38.5% versus 7.4%;  $p = 0.01$ ) at 6 months postrandomization for participants with a history of major depressive episode (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. Covey and colleagues (1999) found a significant treatment by gender by depression interaction. Women with past histories of MDD 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. Men who were MDD history positive did not have higher quit rates on naltrexone.

**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?

Most included trials 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. 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 compared to placebo control.

## FUTURE RESEARCH RECOMMENDATIONS

While this review provided some evidence of smoking cessation strategies for patients with depression, more work is needed in this area. Principally, we found very little trial data on intervening with smokers with current 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 and may lead to better treatment matching. In many instances, we were able to address only the incremental benefit of adding one strategy to an intervention package (e.g., behavioral counseling with or without antidepressant). Future studies should be designed to allow for direct comparisons between combinations of likely efficacious therapies for smokers with depression such as combination NRT therapy. Also, we were unable to disaggregate multicomponent interventions. Future research should be designed to disentangle active ingredients of interventions and optimize dose, duration, frequency, and sequencing of smoking cessation strategies. Finally, future research should be conducted to characterize adverse effects of treatments, including changes in negative affect and depressive symptoms.

## **CONCLUSIONS**

In conclusion, the peer-reviewed literature contained few randomized controlled trials of smoking cessation interventions for patients with depression. Most trials excluded patients with current or recent MDD. Thus, most of the data for this evidence review were from subgroup analyses of patients with depressive symptoms or remote histories of depressive disorder. However, the majority of reports included in this evidence review were of good quality and had consistent results. We found insufficient evidence to characterize adverse effects of treatments and examine moderator effects of gender, depression status, and treatment delivery sequencing.

However, this evidence review lends support for several promising interventions. Our results support a small, positive effect for adding behavioral mood management counseling to smoking cessation cotreatments. Smokers with depression may respond better to smoking cessation interventions augmented with mood management techniques. Evidence also shows support for adding NRT; however, included trials were too varied to be analyzed quantitatively. All of the included antidepressant trials showed small, positive effects, but a summary estimate of effect was not statistically significant. However, there was heterogeneity in antidepressant type across studies. Effects likely vary with medication type. Health care providers should consider encouraging their patients with depression who smoke to seek smoking cessation services that include NRT and also address behavioral mood management counseling.