

Depression and smoking cessation: Does the evidence support psychiatric practice?

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Abstract: Depression and smoking are highly comorbid. The vast majority of psychiatrists treating depressed patients do not target or treat nicotine dependence, and many inpatient psychiatric facilities implicitly condone smoking by providing 'smoke breaks'. The reasons for failure to treat are unclear, but are probably linked to the notion that depressed smokers are neither willing nor able to quit, and will become more depressed if they try. We review the clinical evidence on depression and smoking cessation, and find little support for current psychiatric practice. Although quitting smoking does appear to pose a risk for the development of depression, this risk is not clearly higher in those with a past history of depression than those without. Depressed smokers are as capable as nondepressed smokers of quitting smoking, and at least one-quarter of depressed smokers is willing to try. Sustained abstinence may even lead to improvement in depressive disorders. More research is needed to understand the relationship between depression and quitting smoking, but current clinical evidence suggests more resiliency among depressed smokers than common clinical wisdom would dictate.

Keywords: depression, smoking cessation, psychiatry, nicotine dependence, withdrawal

Introduction

Nicotine dependence is the most common psychiatric diagnosis in the United States (Bergen and Caporaso 1999). By some estimates, 50%–60% of patients with major depression also suffer from nicotine dependence (Glassman et al 1990). The prevalence of depression among smokers has been estimated at three times that of nonsmokers (Farrell et al 2001). Depression is associated with increased risk of heart disease and diabetes (Plante 2005); and smoking has well-known morbidity associated with it, including cancer, heart disease, and emphysema. Together, depression and smoking may offer greater combined health risk; and women smokers may be especially vulnerable to this combined health risk, as they suffer from depression at a ratio of two to one compared with men.

The American Psychiatric Association recommends integration of smoking cessation treatment with psychiatric care (APA 1996). Despite this imperative, psychiatrists in everyday practice largely ignore smoking. Himelhoch and Daumit found that psychiatrists offered smoking cessation counseling to only 12.4% of the visits for smoking patients (based on 8,451 visits to 573 psychiatrists from 1992 to 1996) (Himelhoch and Daumit 2003). Nicotine replacement therapy was not prescribed at a single visit, nor the diagnosis of nicotine dependence made at any patient visit (Himelhoch and Daumit 2003). However, eighty percent of smokers were diagnosed with a depressive disorder (Himelhoch and Daumit 2003). The reasons for psychiatrists' tendency to ignore nicotine dependence in patients with depressive disorders are not known, but probably relate to the common clinical wisdom that depressed smokers are neither willing nor able to quit smoking, and that any attempt at smoking cessation will precipitate and/or exacerbate depression.

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This review examines the link between depression and quitting smoking, with an eye toward how the evidence supports or fails to support current psychiatric practice. We begin with a brief summary of the data on smoking cessation treatment in nondepressed smokers (ie, smokers with no known depressive disorder), progress to the literature on smoking cessation in individuals with depressive disorders, and finish with a look at treatment interventions designed specifically for depressed smokers (ie, smokers with a diagnosable depressive disorder, past or present). This review attempts to address the following questions: “Are depressed smokers willing and able to quit smoking?”, “Are depressed smokers versus nondepressed smokers more likely to experience depressive symptoms while trying to quit?”, and “Does the data support or refute common clinical practice?”.

Smoking cessation and nondepressed smokers

Although recent CDC data suggest a steady decrease in smoking prevalence among American adults since 1993, an estimated 20.9% (44.5 million) are still classified as current smokers (Maurice 2005). Several smoking cessation interventions have been introduced and approved by the Federal Drug Administration (FDA) over the last two decades, based on research conducted almost exclusively in nondepressed smokers. Effective treatments to date appear to consist of a pharmacological treatment in combination with even a modest psychosocial intervention (Hall et al 2002). We briefly review the data on pharmacological treatments for smoking cessation in nondepressed smokers.

The FDA approved the first nicotine replacement therapy (nicorette gum) for over-the-counter (OCT) consumption in 1996, followed closely by nicotine replacement patches and lozenges. In their small, recommended doses, these OCT therapies, in addition to the prescription only nicotine inhaler and nasal spray, reduce the craving and withdrawal symptoms often associated with smoking cessation. However, as the absorption methods of these therapies vary, some studies have shown a clinical benefit to combining nicotine replacement therapies (NRT) to achieve the most effectual treatment (Henningfield et al 2005). Therefore, NRT that gradually releases nicotine (ie, the nicotine patch) in combination with an acute release therapy (ie, gum, lozenges, inhaler, and nasal spray) provides treatment in which long-term and short term cravings and withdrawal symptoms are better addressed (Sweeney et al 2001).

In addition to nicotine replacement therapies, pharmacological treatments are also recommended during smoking

cessation therapy, and the FDA has approved two first line pharmacological treatments for this purpose. The first, bupropion hydrochloride, is believed to restrain the reuptake of norepinephrine and dopamine with minimal side effects and a high rate of tolerability (Kotlyar and Hatsukami 2002). Although initially promoted for its antidepressant qualities, extensive research has consistently shown bupropion's efficacy as a smoking cessation aid as well (Richmond and Zwar 2003). Hurt and colleagues (1997) published the first controlled trial to examine the efficacy of bupropion as a treatment for nicotine dependence (Hurt et al 1997). In that trial, 615 nondepressed smokers were randomly assigned to placebo or three regimens of bupropion (100 mg, 150 mg, 300 mg). At 12 month follow-up, abstinence rates were as follows: placebo 12.4%; bupropion 100 mg 19.6%; bupropion 150 mg 22.9%; bupropion 300 mg 23.1%.

In perhaps the first study to combine NRT with an antidepressant medication, a trial by Jorenby and colleagues (1999), conducted under the auspices of the manufacturer, compared placebo with bupropion (300 mg), nicotine patch (21 mg), and nicotine patch (21 mg) + bupropion (300 mg). Eight Hundred and thirty-nine nondepressed smokers were randomized. Treatment lasted seven weeks with a 2-week tapering phase. Participants met weekly for testing and to receive counseling interventions. Point prevalence abstinence rates at 12-month follow-up were as follows: placebo 15.6%; nicotine patch 16.4%; bupropion 30.3%; bupropion + nicotine patch 35.5%. These findings suggest once again that a combination of smoking cessation interventions produce more significant abstinence rates (Jorenby et al 1999).

The nicotinic acetylcholine receptor partial agonist varenicline tartrate is the second and most recently FDA approved pharmacological treatment for smoking cessation. In two randomized, double-blind, placebo-controlled clinical trials conducted by Gonzales and colleagues (2006) and Jorenby and colleagues (2006), varenicline was compared with bupropion and placebo to determine its efficacy. Overall, the abstinence rates from both studies demonstrated that varenicline was more effective than both bupropion and placebo at short-term and long-term time follow-up (Gonzales et al 2006; Jorenby et al 2006).

In the trial conducted by Jorenby and colleagues (2006), 1,027 nondepressed smokers received brief smoking cessation counseling (≤ 10 min) per US Public Health Services guidelines, in combination with one of the following: varenicline (titrated to 1 mg twice per day), bupropion sustained release (SR) (titrated to 150 mg twice per day), or placebo, during the 12 week treatment period, followed

by 40 weeks nonpharmacological follow-up. The four week continuous abstinence rates for weeks 9 through 12 were as follows: varenicline 43.9%, bupropion SR 29.8%, and placebo 17.6%. The continuous abstinence rates for weeks 9 through 52 were as follows: varenicline 23%, bupropion SR 14.6%, and placebo 10.3% (Jorenby et al 2006).

Similarly, Gonzales and colleagues (2006) enrolled 1,025 nondepressed smokers in their randomized, double-blind, placebo-controlled study. In this trial, participants were randomly assigned to receive brief smoking cessation counseling (≤ 10 min) per US Public Health Services guidelines, as well as varenicline (titrated to 1 mg twice per day), bupropion SR (titrated to 150 mg twice per day), or placebo during the 12 week treatment period, followed by 40 weeks nonpharmacological follow-up. The four week abstinence rates for weeks 9 through 12 were as follows: varenicline 44.0%, bupropion SR 29.5%, and placebo 17.7%. The continuous abstinence rates for weeks 9 through 52 were as follows: varenicline 21.9%, bupropion SR 16.1%, and placebo 8.4% (Gonzales et al 2006).

Nortriptyline has been endorsed by the US clinical practice guideline and the agency for health research quality (AHRQ) as a second-line smoking cessation therapy (Henningfield et al 2005), although it is not FDA approved as such. Hall and colleagues (1998) combined the tricyclic antidepressant nortriptyline or placebo with an intensive, clinic-based behavioral treatment program and found the 64-week continuous abstinence rate produced by nortriptyline was double that for placebo (24% vs. 12%). Nortriptyline was also superior to placebo in a second study conducted by Prochaska and colleagues (1998), although the 6-mo point prevalence abstinence rates for both active and placebo conditions were low (nortriptyline 14%; placebo 3%).

Perhaps in light of the promising results produced by the antidepressants bupropion and nortriptyline, researchers have studied the effectiveness of other antidepressants for smoking cessation as well. In a recent study by Niaura and colleagues (2002), 989 nondepressed smokers were assigned to a 10-week trial of the serotonin reuptake inhibitor fluoxetine or placebo coupled with a clinic-based, individualized behavioral intervention. Mean abstinence rates were not reported but survival analysis suggested that fluoxetine resulted in an improved response-to-treatment. Interestingly, fluoxetine plasma levels were associated with survival time. However, in a recent literature review of multiple studies on this subject, Hughes and colleagues (2004) found very little evidence to suggest a long-term benefit of serotonin reuptake inhibitors, atypicals, and monoamine oxidase inhibitors as

smoking cessation aids in nondepressed populations. In turn, these data imply that the mechanism by which bupropion and nortriptyline function as smoking cessation aids is independent of their antidepressant qualities.

Smoking cessation and depressed smokers

Depressed smokers are an understudied population. They are typically excluded from smoking cessation trials. Most studies designed specifically to examine the effectiveness of a given treatment for smoking cessation, exclude individuals with depression (Hurt et al 1997; Jorenby et al 1999; Jack et al 2003). The paucity of clinical research in this area, despite the strong epidemiologic link between depression and smoking, is likely related to the premise that depressed smokers will not accept or tolerate smoking cessation interventions.

Are depressed smokers willing to stop smoking? Prochaska and colleagues (2004) showed that in fact about a fourth of depressed smokers surveyed were eager to quit smoking, and were willing to take action to quit within 30 days. This study also found that depression severity and history of depression recurrence were not related to willingness to try to quit smoking among depressed outpatients. Haug and colleagues (2005) showed that 53 of 154 depressed smokers were willing to embark on a smoking cessation treatment plan that included behavioral counseling, nicotine patch, and bupropion. Haug and colleagues also found that severity of depression symptoms and depression history were unrelated to acceptance of smoking cessation treatment. On the other hand, few chronic psychiatric inpatients are ready to try to quit smoking (Hall et al 1995).

Are depressed smokers able to stop smoking? Data are mixed on the effects of depression severity or history of depression on quit rates. Anda and colleagues (1990) showed in an epidemiologic, cross-sectional study, that smokers with higher depression scores at the start of smoking cessation treatment were less likely to have quit eight years later than smokers not depressed at baseline (10% vs 18% quit). However, John and colleagues (2004), in a cross-sectional analysis of 4,075 smokers with past (lifetime) or current (12-month) diagnosis of depression, showed no difference in smoking cessation three years later compared to those without a mood disorder. A recent meta-analysis by Hitsman and colleagues (2003), looked at 15 published studies and found no difference in either short-term (less than 3 months) or long-term (greater than 6 months) abstinence rates between smokers positive versus negative for history of depression. A study of the effect of baseline depressive symptoms

on smoking outcomes in 600 African American smokers, found that baseline depression also did not correlate with cessation rates at study endpoint (Catley et al 2005). The preponderance of the evidence implies that depression does not adversely affect smoking quit rates; ie, smokers with depressive disorders are able to quit smoking at the same rates as nondepressed smokers.

The progression of depressive symptoms over the course of smoking cessation treatment, appears to be a more consistent negative correlate of quitting smoking. Killen and colleagues (1996) have shown that worsening of depression during smoking cessation treatment, even in subjects who do not meet criteria for major depression at start of treatment, predicts a worse outcome in quitting smoking. Others have also found that individuals who become depressed while trying to quit smoking, are less likely to be successful at quitting (Cinciripini et al 2003; Levine et al 2003; Catley et al 2005). Burgess and colleagues (2002) have demonstrated that a delayed increase in depressive symptoms during smoking cessation treatment, as oppose to an initial short-lived increase or a steady decrease, is associated with lower quit rates. This is an interesting finding, implying that dysphoria in the acute withdrawal period may be different from dysphoria that begins or progresses after acute withdrawal has abated.

In summary, smoking quit rates are not clearly associated with prior history of depression, depressive symptoms at the start of smoking cessation treatment, or even necessarily briefly depressed mood in the acute withdrawal period. However, the trajectory of mood symptoms over the course of smoking cessation treatment does appear to impact quit rates: namely, worsening of depression after quitting appears to be a risk-factor for poor smoking outcomes. So who is likely to get depressed while quitting? Common clinical wisdom holds that individuals with history of depression are particularly vulnerable to worsening mood symptoms during smoking cessation. What is the evidence to support the notion that depressed smokers are more vulnerable to depression while quitting than nondepressed smokers?

A study by Glassman and colleagues (2001) examined 76 smokers with a past history of major depressive disorder, all euthymic and off of antidepressant medication at the start of smoking cessation treatment, in order to determine the rates of recurrent depression in abstainers versus nonabstainers. Subjects were enrolled in a 2-month smoking cessation trial, and recurrence of major depression was assessed by structured clinical interviews at three and six month intervals. Thirteen of 42 successful abstainers had a recurrence of major depression; whereas

two of 34 smokers had a recurrence of major depression. The findings demonstrate that depressed smokers who quit smoking are more likely to relapse to depression than depressed smokers who keep smoking; but only a minority of depressed smokers will get depressed. The study did not include a comparison group of nondepressed smokers, and so does not address the question of whether depressed smokers are at higher risk for depression than nondepressed smokers during quitting.

Covey and colleagues (1997) compared the rates of occurrence of major depression with smoking cessation, among smokers with no prior diagnosis of depression, smokers with one prior major depressive episode, and smokers with recurrent major depressive disorder (Covey et al 1997). Smokers who succeeded in abstaining from cigarettes for a 10-week smoking cessation program, were followed up three months after quitting (N = 126), and assessed for a major depressive episode using DSM-III-R criteria. Two of 91 subjects with no history, four of 24 subjects with past single major depression, and three of 10 subjects with past recurrent major depression, developed a major depressive episode by 3-month follow-up. In the absence of a comparison between those who did and did not successfully quit smoking, the results of the study are difficult to interpret. Those who continued smoking might have relapsed to major depression at the 3-month follow-up at the same rates as those who quit, given the recurrent nature of depressive disorders, particular in the absence of treatment. Nonetheless, the study does provide some preliminary evidence that those with prior depressive disorders, who quit smoking, are more likely to have a major depressive episode in the months following smoking cessation, than those with no prior depression history.

Even more remarkable is the apparent resiliency of smokers with depressive disorders in the face of smoking cessation, a significant physical and psychological stressor. The covey study found that 24 of 34 smokers, more than two-thirds the sample with a prior diagnosis of major depression, did not have a recurrence of major depression after quitting smoking, even without antidepressant medication or other apparent intervention. Two of the subjects who did have a recurrence of depression, experienced depressive symptoms for only two days before restarting effective antidepressant therapy.

In a study by Covey et al, placebo was compared with bupropion for smoking cessation treatment (N = 429). Depressive symptoms were measured at weeks 8 and 12.

Changes in depressive symptoms were measured at these endpoints, and did not differ for those with and without a past history of depression (Cox et al 2004).

The clinical studies reviewed above have included depressed smokers who were euthymic (ie, not depressed) at the initiation of smoking cessation treatment, and not on antidepressant therapy. Presumably, these individuals had a less severe form of depression, since they were able to be well without treatment for depression for some period of time. To our knowledge, smokers who are depressed at baseline, on or off medication, and smokers with more severe forms of depression, have not been included in smoking cessation studies comparing clinical outcomes with nondepressed smokers.

Is there any evidence that stopping smoking actually improves depression? Burgess and colleagues (2002) found that of 163 smokers with a past history of depression, 40% experienced an increase in depression symptoms during quitting, and 47% experienced a decrease in depression symptoms during quitting. In a national household survey on drug abuse (N = 13,827), although current smokers were found to be at highest odds for suffering from depression, followed by former smokers, followed by nonsmokers; odds of depression were lower with more elapsed time since last smoking (Martini et al 2002). Thorsteinsson and colleagues (2001) used nicotine replacement therapy in smokers who were depressed at the initiation of smoking cessation treatment, independent of past history of depression, and examined both smoking and mood outcomes. One patient in the placebo group (N = 20), and no patients in the nicotine group (N = 18), became more depressed; and there was a trend for improved mood symptoms in those subjects who remained abstinent from cigarettes for 29 days. This study was limited by small sample size. A study by Kahler and colleagues (2002) looked prospectively at 179 smokers with a history of major depression, and found that continuous abstinence was associated with short- and long-term reductions in depressive symptoms (Kahler et al 2002). Although limited, these data suggest that abstinence may contribute to mood gains.

Improved mood with sustained abstinence from cigarettes may be related to brain serotonin levels. A study by Malone and colleagues (2003) showed an inverse relationship between amount of cigarettes smoked and serotonin function, as measured by fenfluramine challenge tests and cerebrospinal fluid levels of 5-hydroxyindoleacetic acid. Another potential explanation for improved mood with smoking cessation is a decrease in hypercholinergic neurotransmission

at the nicotinic acetylcholine receptors (nAChR) (Shytle et al 2002).

Combined treatments for smoking cessation and depression

Based on the evidence reviewed above, if mood symptoms could be effectively targeted during smoking cessation treatment, then depressed smokers, or more accurately depressed quitters, would have a better chance at cessation. Several studies have researched smoking cessation interventions designed specifically for depressed smokers. We examine these sparse data below.

A study in African American smokers demonstrated benefit of bupropion on mood during smoking cessation treatment (Ahluwalia et al 2002); and a follow-up study suggested that bupropion may facilitate smoking cessation in part by reducing depressive symptoms (Catley et al 2005). However, even in this study, the authors concluded that bupropion's primary mechanism of action is not related to its antidepressant efficacy, even among the more depressed smokers.

In a group of sub-clinically depressed smokers, Lerman and colleagues (2004) found that highly nicotine dependent smokers (score of six or more on the fagerstrom test for nicotine dependence) receiving bupropion 300 mg for smoking cessation, had a significant improvement in depressive symptoms compared to highly nicotine dependent smokers on placebo. Once the smoking cessation treatment protocol was over and bupropion/placebo discontinued, those who stopped bupropion got significantly more depressed than those who stopped placebo. The effect of bupropion on mood held true only for the high dependence nicotine group, not the low dependence group. This study implies that highly dependent smokers are more likely to have a positive mood response to bupropion, and may need to continue bupropion longer than the usual 10–12 week recommended course. Whether the bupropion is directly mediating mood, or mediating some component of nicotine dependence affecting mood, is unclear.

Brown and colleagues (2001) found that for a subset of smokers with past recurrent major depression and high nicotine dependence, a cognitive behavioral therapy directed specifically for depressed mood led to higher abstinence rates than standard CBT for smoking cessation. A study by Haas and colleagues (2004) also supports the use of CBT over health education in smokers with a past history of major depression.

Covey and colleagues (2002) designed a study looking at the use of sertraline, a serotonergic antidepressant,

specifically in the treatment of depressed smokers. Smokers with a history of major depressive disorder ($N = 134$) and varying degrees of depressive symptomatology at baseline, were randomized to receive sertraline or placebo over a 9 week period, combined with intensive individual weekly counseling. Sertraline proved to be more effective than placebo in ameliorating the acute withdrawal symptoms of irritability, anxiety, and craving, but no more effective than placebo in terms of abstinence rates.

The limited data suggest that smoking cessation treatments modified to target depressed mood, may improve abstinence rates for certain subpopulations of smokers. The interplay between mood and degree of nicotine dependence may be an important predictor of the progression of depression while quitting (Pomerleau et al 2005). Highly nicotine dependent smokers may have a more profound and protracted withdrawal, which can mimic and possibly even lead to depression; and/or stopping smoking may unmask an underlying depressive disorder in individuals who were not previously symptomatic.

Conclusions and future directions

Most psychiatrists do not address or treat smoking in depressed patients, presumably because they anticipate that depressed smokers will be unwilling to quit, unable to quit, and that smoking cessation will cause or exacerbate depressive symptoms. The evidence does not clearly support this bias. At least a quarter of nonhospitalized psychiatric patients with a diagnosis of a depressive disorder are willing to try and quit smoking. Past history of depression, and even depressive symptoms at the start of smoking cessation treatment, do not consistently negatively impact quit rates. Depressed smokers may be at higher risk to experience depression with smoking cessation than nondepressed smokers, but the data is equivocal. Abstinence from cigarettes for prolonged periods may be associated with a decrease in depressive symptomatology.

A minority of smokers will enter a major depressive episode during or shortly after quitting smoking. The trajectory of mood symptoms after quitting appears to be a sensitive predictor of relapse. More research is needed to explore which individuals will become depressed after quitting; and what treatment methods should be used to target smoking cessation-induced depression. More research on the impact of mood at baseline, including severity and specificity of depressive symptoms, would help clarify which types of smokers are most vulnerable to depression during smoking cessation. Future studies should also try to elucidate what

other variables besides mood contribute to poor mood trajectory and lower cessation rates. The data point toward nicotine dependence as an important contributing variable: highly nicotine dependent smokers are potentially at higher risk for depression and relapse, but also more responsive to bupropion. Preliminary evidence supports the development of specific smoking cessation treatments tailored for depression, over standard smoking cessation therapies.

A review of the evidence highlights the resiliency of depressed smokers in the face of smoking cessation, contrary to common clinical wisdom. When one considers the potential gain in offering smoking cessation treatment to individuals with depressive disorders, including the potential for decreased morbidity and mortality from both nicotine dependence and depression; the risk of depression may well be worth taking, and certainly worth discussing with patients. And who better to provide smoking cessation treatment, than psychiatrists and other mental health care practitioners who are experienced in the treatment of depressive disorders?

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