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Smoking and Depression: Is Smoking Cessation Effective?

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Abstract

Patients with depression tend to have a higher rate of smoking and an increased severity of nicotine dependence. It seems that common genetic and environmental factors may influence the bimodal relationship between smoking and depression. Nicotine has some positive reinforcing/rewarding effects that may affect people with mood disorders and smoking is also used as a 'relief medication' in order to ameliorate symptoms of depression, as it is already known that nicotine, which is the major psychoactive ingredient in tobacco, may act as an antidepressant. To date, the data regarding the difficulty in smoking cessation in depressed smokers are conflicting. Low confidence and self-esteem among this group of smokers are significant predictors of failure during smoking cessation attempt. In the most recently published guidelines for smokers with psychiatric comorbidities the suggestion is for combination treatment (counseling and pharmaceutical treatment) and prolongation of a therapeutic approach.

Introduction

It is already known that the historically high rates of smoking among smokers with mental illness are associated with high morbidity and mortality rates related to tobacco [Williams and Ziedonis, 2004]. Additionally some myths about smoking cessation in mentally ill smokers may present as barriers for the effective treatment of smoking addiction. In this review we discuss the relationship between smoking and depression, the influence of depression on smoking cessation trial and the available therapies for smoking cessation in this group of smokers.

Smoking and Depression

There are currently strong epidemiological data of comorbidity between smoking and depression [Rondina *et al.* 2007]. Patients with depression tend to have a higher rate of smoking than the general population and smoke twice as many cigarettes as smokers without mental illness [Lasser *et al.* 2000]. Among patients with major depression or those with clinically significant depressive symptoms, smoking prevalence is 40-60% [Kalman *et al.* 2005]. As a result, depressed smokers tend to die 25 years younger than the general population by smoking-related illnesses, such as heart and lung diseases [Colton and Mandersheid, 2006]. Additionally, the severity of nicotine dependence, estimated by either the number of nicotine withdrawal symptoms or the Fagerstrom test, is found to be increased in case of psychiatric disorders [John *et al.* 2004].

Correlation Between Smoking and Depression

Box 1. Correlation between smoking and depression.

Common genetic factors
Common environmental factors
Nicotine's effect on neurochemical systems of the brain
Smoking is used as a 'relief medication'
Nicotine has positive reinforcing/rewarding effects.

The relationship between smoking and major depression is reciprocal. Nicotine dependence might facilitate the onset of psychiatric disease, such as depression, and depression might also affect to the maintenance of dependence [John *et al.* 2004]. In addition, due to the fact that cigarette smoking accelerates the metabolism of many antidepressant drugs, higher levels of medication are necessary if smoking status changes [Hall, 2007].

Common genetic and environmental factors may influence the relationship between smoking and depression [Albers and Biener, 2002]. In a study with dizygotic and monozygotic twins, the family history of smoking or depression predicted the risk for major depression or smoking, respectively [Kendler *et al.* 1993]. Another study by Choi *et al.* [1997] has investigated whether

cigarette smoking in adolescence predicts the development of depressive symptoms. Their data suggest that smoking status was the most significant predictor of developing depressive symptoms independently of other personal or familial factors.

According to another aspect smoking is used as a 'relief medication' in order to ameliorate symptoms of depression and this behavior may lead gradually to nicotine dependence [Repko *et al.* 2007; Fergusson *et al.* 2003]. On the other hand, nicotine dependence in turn may increase individual susceptibility to depression [Goodman and Capitman, 2000].

Nicotine has also some positive reinforcing/rewarding effects that may affect people with mood disorders. For example individuals with attention deficits may smoke in an attempt to self-medicate this deficit, as a study by Baschangel and Hawk [2008] has shown. The effect of nicotine on controlled early focused attention appears to be related to baseline attention processing. Individuals with poorer attention may benefit more from nicotine [Baschangel and Hawk, 2008]. By using functional MRI in order to determine the neural substrates of nicotine's effects on a sustained attention it was found that performance was associated with activation in a fronto-parietal-thalamic network. Mildly abstinent smokers showed less brain activation in the parietal cortex, which was improved after transdermal nicotine replacement. Nicotine also induced a generalized increase in occipital cortex activity. By activating these areas nicotine may improve attention [Lawrence *et al.* 2002].

Psychoactive Properties of Nicotine

The findings of associations between smoking and depression suggest that the neural substrates of smoking and antidepressant medication may overlap. It is well recognized that nicotine is the major psychoactive ingredient in tobacco and may act as an antidepressant. Both acute and chronic use of nicotine significantly improves the performance of experimental rat model independently of locomotor activity [Vazquez-Palacios *et al.* 2004; Tizabi *et al.* 1999].

Nicotine acts on dopamine systems, which are critical for a variety of behavioral systems from motor function to reinforcement and cognitive function. In humans the cognitive improvement induced by nicotine treatment is primarily seen with attention whereas in rats is seen with the improvement of performance [Levin *et al.* 2006]. The central effects of nicotine are also mediated by the nicotinic cholinergic receptors that are widely distributed in the brain [Tapper *et al.* 2004]. Nicotine can indirectly act as a muscarinic agonist by stimulating the release of acetylcholine. It is of interest that central cholinergic systems have also been implicated in depression. This might suggest that the link between smoking and depression can be through central cholinergic systems [Janowsky and Risch, 2003]. Similarly, cholinergic systems may be altered in persons with attention-deficit/hyperactivity disorder (ADHD) and it has been shown nicotine may alleviate ADHD symptoms [Potter *et al.* 2006]. Additionally, according to experimental data in rats, nicotine induces, in a dose-dependent manner, the release of serotonin, probably through its action on serotonin receptors [Mihailescu *et al.* 1998]. Considering that most antidepressant therapies act by improving the bioavailability of serotonin this might be one more mechanism of the antidepressant action of nicotine.

Although nicotine is the major psychoactive ingredient in tobacco smoke, other tobacco constituents such as acetaldehyde and monoamine oxidase inhibitors (MAOIs) also may play an important role in facilitating and potentiating the rewarding actions of nicotine. MAOIs have been used for the treatment of depression. When adolescent and adult rats were treated with MAOIs, they respond with increased and robust self-administration of nicotine. So, other components of tobacco known to have antidepressant effects may contribute to the self-medicating effects of smoking [Gehricke *et al.* 2007].

Although there is evidence confirming the coexistence between smoking status and depression, it is to date unclear whether it is depression that leads to heavy smoking condition or whether it is smoking attitude that predisposes to depression. Further studies are needed to clarify this relationship. This may have two important implications: if smoking influences the susceptibility to depression then smoking cessation might be accompanied by a reduction in depression in the long term. Conversely, if depression leads to smoking then one might expect that the successful treatment of depression would also be accompanied by a reduction in smoking.

Depression and Smoking Cessation: Does Depression Influence the Success of Smoking Cessation Trial?

Box 2. Depression and smoking cessation.

Increased incidence of post-cessation depressive symptoms
Women have lower success rates in smoking cessation because of higher rates of depression among them
Depression is a risk factor for smoking relapse after cessation
Smokers with depression show similar chronic abstinence rates as the general population independently on their failure early on their quit attempt
Depressed smokers do not differ in their motivation to quit smoking than the general population
Low self-esteem among depressed smokers affects negatively their smoking cessation trial

At present, there is conflicting evidence as to whether depression is associated with greater difficulty in quitting smoking [Hitsman *et al.* 2003; Smith *et al.* 2003]. In a recent study, smoking cessation was evaluated in smokers with either a history of or current depression and smokers without such a history. Surprisingly smokers with current depression had lower smoking abstinence at the end of the first week of a smoking cessation trial than those with only a past history or no history of depression. However, this fact was not predictive of the final outcome [Japuntich *et al.* 2007].

This could be due to the fact that nondepressed smokers tend to put all their effort into stopping smoking early in the cessation process and stick to their quitting date. Failure to achieve this target may diminish their self-efficacy and influence their final smoking cessation goal. On the other hand, depressed smokers do not expect to quit completely and immediately during the first weeks, so even a reduction on the numbers of cigarettes may be a partial success which reinforces them to continue their smoking cessation attempt [Parrott, 2004].

Does Smoking Cessation Correlate With the Appearance of Depression?

History of major depression clearly increases the risk of post-cessation depressive symptoms. Specifically, the incidence of major depression over 2-12 months post-cessation was 0-14% among all smokers trying to quit and 3-24% among smokers with a past history of major depression. However, the post-cessation course of depression over a long period of time remains still unclear [Hughes, 2007].

In a meta-analysis, Covey *et al.* [2006] attempted to provide further data on the effect of past major depression history on smoking cessation. They found that the dissimilar findings among studies concerned with the frequency of major depression episodes during the quitting attempt are not explained merely by the number of past episodes, but also by the age at onset of the first episode, the number of symptoms met during the episode and the duration of the episode. According to this evidence the level of depressed mood must be considered in the beginning of the smoking cessation course together with the initial evaluation of nicotine dependence [Covey *et al.* 2006].

This is supported by another study in which smokers with single major depression history did not manifest a smoking cessation deficit compared with smokers with no major depression history. On the other hand smokers with a history of recurrent major depression showed an abstinence rate that was significant lower than in those with single major depression history [Hitsman *et al.* 2003].

Factors Associated With Failure to Stop Smoking in Depressed Smokers

Gender Influence on Depression and Its Relation to Smoking Cessation

The influence of depression on smoking cessation is influenced by gender, as women tend to have higher rates of major depression than men [Husky *et al.* 2008; Smith *et al.* 2003]. Among daily smokers, women are more likely to meet criteria for current depression compared with men. Additionally, increased risk for depression is described in women compared with men among nondaily smokers [Husky *et al.* 2008].

Women have lower success rates in smoking cessation attempts and are more likely to experience withdrawal depressive symptoms [Killen *et al.* 2003]. Apart from the greater likelihood of depression, women may face different stressors and barriers to quitting such as weight control concerns, hormonal cycles, greater nonpharmacologic motives for smoking (socialization) and educational differences. This suggests that women may benefit from tobacco dependence treatments that address these issues [Fiore *et al.* 2008]. In a study that examined the generalizability of gender differences in abstinence found that abstinence was unaffected by controlling the treatment or time of relapse. It was concluded that additional studies are needed in order to elucidate the relation between gender and abstinence [Wetter *et al.* 1999].

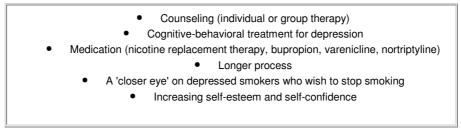### Self-esteem, Self-confidence and Motivation

Low confidence and self-esteem among depressed smokers is a significant predictor of failure during smoking cessation attempts. An interesting study among adolescents found that smokers had lower self-esteem than nonsmokers. Among adolescent smokers, girls had lower self-esteem than boys when nicotine dependence level was low (Fagerstrom score ≤3). However, this gender difference was not observed in smokers with moderate or high nicotine dependence (Fagerstrom score ≥4) where mean self-esteem was uniformly low [Guillon *et al.* 2007].

In study by Haukkala *et al.* [2000] it was found that depressed smokers were not different regarding their readiness to quit smoking compared with nondepressed smokers and, in contrast, subjects with higher depression scores were more motivated. Higher depression scores were related to lower smoking cessation self-efficacy and this in turn negatively affected the final outcome of the trial. Education level did not influence the association between depression and smoking status [Haukkala *et al.* 2000]. Turner *et al.* [2008] reported that self-efficacy and motivation were important predictors of cessation in the general

population. This evidence suggests that a fruitful discussion to increase the self-esteem of the participants is crucial for a successful outcome of smoking cessation in smokers with psychiatric comorbidiy.

Therapeutic Interventions for Depressed Smokers

Box 3. Therapeutic interventions for depressed smokers.

- Counseling (individual or group therapy)
- Cognitive-behavioral treatment for depression
- Medication (nicotine replacement therapy, bupropion, varenicline, nortriptyline)
- Longer process
- A 'closer eye' on depressed smokers who wish to stop smoking
- Increasing self-esteem and self-confidence

According to international guidelines for smoking cessation in clinical practice [Rigotti, 2002], there are two approaches with strong scientific evidence: (1) counseling (individual or group); and (2) pharmaceutical treatment. Medication approved for smoking cessation as first-line treatment includes: nicotine-replacement products (NRTs); bupropion; the most recent approved agent, varenicline; and nortriptyline; with clonidine as second-line treatment [Jorenby *et al*. 2006].

In the most recently published guidelines for smokers with psychiatric co-morbidities the suggestion is for a combination treatment and prolongation of therapeutic approach in order to reduce dropout rates given the possibility of deterioration of depressive symptoms [Gelenberg *et al*. 2008]. All smokers with psychiatric disorders should be offered tobacco dependence treatment and clinicians must overcome their reluctance to treat this population, although some clinicians may wish to offer this treatment when psychiatric symptoms are not severe [Fiorre *et al*. 2008].

Treatment With Bupropion

According to a recent review of the literature, in assessing the use of antidepressants in smoking cessation, bupropion and nortriptyline were the only medications effective in long-term smoking cessation. Based on this review, bupropion and nortriptyline appear to be equally effective and of similar efficacy to nicotine replacement therapy. Combination therapy of bupropion or nortriptyline with nicotine replacement therapy did not provide any additional long-term benefit [Hughes *et al*. 2007].

When bupropion was administrated to depressed smokers and its efficacy was compared to nicotine-replacement therapy (transdermal patch nicotine) and to placebo, bupropion was found to be superior with regard to smoking cessation than placebo and nicotine patches. Bupropion was especially effective for female smokers, a subpopulation with a greater percentage of depression compared with male smokers. A significant finding of that study was that when nicotine patches were administrated alone, they did not significantly improve abstinence rates compared with placebo. Similarly, abstinence rates for the combined bupropion and nicotine patch were not significantly higher than rates produced by bupropion alone [Smith *et al*. 2003].

With regard to the possibility of deterioration of depressive mood during the smoking cessation trial, smokers with high nicotine dependence when they receive bupropion treatment are more likely to present less depressive symptoms during active treatment. However, they experience a rebound of depressive symptoms when bupropion is discontinued [Shiffman *et al*. 2000].

The use of this medication for treating nicotine dependence in children and adolescents with psychiatric disorders needs to be very careful. Antidepressants may increase the risk for suicidal ideation and behavior in this age group [Nides, 2008]. The available experimental studies of youth cessation interventions find that behavioral interventions increase the chances of youth smokers achieving successful cessation [Curry *et al*. 2009].

The possible mechanisms by which bupropion affects smoking cessation and the withdrawal symptoms of depressed smokers are not yet clear. It seems that bupropion's effectiveness is not due to its antidepressant action. Although it has been speculated that the antidepressant effects of bupropion are due to the selective inhibition in the reuptake of dopamine and noradrenaline in the brain, studies on nondepressed smokers had similarly positive results and thus the above theory has been abandoned [Brown *et al*. 2007].Bupropion has noradrenergic activity and, to a lesser extent, dopaminergic activity, which may result in activation and mood elevation, or may partially mimic nicotine effects [Shiffman *et al*. 2000].

Treatment With Other Antidepressants

In an assessment of the effectiveness of other antidepressant medication (serotonin reuptake inhibitors, monoamine oxidase inhibitors, fluoxetine, sertraline, paroxetine, moclobemide and venlafaxine) in long-term smoking cessation therapy, it was found that none of them had any significant long-term effect and the existing literature does not support the use of them for smoking

cessation [Hughes *et al.* 2007]. In contrast, if a patient, who has been successfully treated for depression and has been stable for the past year, decides to quit smoking, the clinician should continue his antidepressant medication for at least 6 months or longer. The smoking cessation therapy should be added to his antidepressant therapy, in order to avoid any deterioration of depressive symptoms [Gelenberg *et al.* 2008]. An important issue to remember is the fact that when a person quits smoking, the metabolism of antidepressants slows down and drug blood levels may increase, increasing the risk of side-effects [Hall, 2007].

Can Cognitive Behavior Treatment Add to Smoking Cessation?

The administration of intensive cognitive-behavioral treatment and bupropion used independently or in combination was investigated in smokers with a history of depression. Adding cognitive-behavioral treatment for depression to standard cognitive-behavioral smoking cessation treatment did not offer extra benefit [Haas *et al.* 2004]. A limitation of this study is the fact that the population of smokers had low scores of depression and therefore we don't know if cognitive-behavioral treatment for depression could be more beneficial in smokers with higher depression scores. In a previously published study it has been shown that this type of treatment is effictive only for smokers with recurrent major depression [Lerman *et al.* 2004].

Varenicline Administration in Depressed Smokers

There are not many studies in the literature that evaluate the administration of varenicline in smokers with depression. A recent study compared the efficacy and safety of varenicline with nicotine replacement therapy among smokers with mental illnesses. The results showed that, with routine psychological and behavioral support, varenicline is more effective in those with mental illness. This was thought to be due to better control of urges to smoke with varenicline use. As far as the adverse events and withdrawal symptoms in those with a mental illness are concerned, there was no evidence of more symptoms or greater deterioration in depressed mood with varenicline than with nicotine replacement therapy [Stapleton *et al.* 2007].

To the best of our knowledge, there is only one report in the literature that described a case of patient with bipolar disorder having a manic episode one week after starting varenicline. The symptoms weakened after the discontinuation of the drug. This exacerbation was attributed to the release of catecholamines, such as dopamine, by varenicline. The imbalance in cholinergic and adrenergic tone has been postulated in the pathophysiology of bipolar disorder [Kohen and Kremen, 2007].

Prevention of Relapse in Depressed Smokers

An important issue in nicotine addiction management is the prevention of relapses. According to most studies on smokers it seems that depression is a risk factors for smoking relapse and is a weak predictor of long-term smoking abstinence [John *et al.* 2004; Murphy *et al.* 2003].

Unfortunately, there are not enough studies for the prevention of the relapses for smokers with mental health disorders. In the study by Smith *et al.* [2003] it was found that sustained-release bupropion improves abstinence rates for smokers with and without a history of depression at 1-year follow-up compared with placebo and nicotine patch alone (29.4% *versus* 8.0% and 6.8%, respectively).

According to general guidelines for smoking cessation, clinicians should provide brief relapse prevention treatment for recent quitters by reinforcing the patient's decision to quit, review the benefits of quitting and assist the patient in resolving residual problems arising from quitting [US Public Health Service, 2000]. The evidence to date does not support the adoption of skills training or other specific interventions (extended treatment contact, imaginary cue exposure, aversive smoking and social support, drug treatments) to help individuals who have successfully quit smoking to avoid relapse. This is an important area for future study, especially in the subpopulation of smokers with a past or current history of depression [Lancaster *et al.* 2006]

Conclusively, the good news is that more approaches, pharmacologic and psychosocial, are available to help people, including psychiatric patients, to stop smoking without adversely affecting their mental health, with special care taken during the first month of treatment [Prochaska *et al.* 2008]. Physicians and psychiatrists seem to have a more therapeutic approach to the ability of patients to quit smoking. According to the evidence patients have to address smoking issues and increase their self-esteem to quit smoking. Smoking cessation might be successful if a longer process for patients with serious mental illness is followed, thus clinicians have to be more optimistic and need to repeat prompts and motivation often (Table 1).

Table 1. Efficacy of smoking cessation interventions in depressed smokers: smoking cessation rates at the end of treatment.

Study	Smoking cessation intervention				
	NRTs	Bupropion	Bupropion + NRT	Varenicline	Nortriptyline
Smith *et al.* (2003)					
DS	29.5%	52.9%	72.1%		
NDS	44%	59.1%	64.9%		
Stapleton *et al.* (2007)					
DS	55.2%			71.7%	
NDS	61.3%			72.1%	
Japuntich *et al.* (2006) (plus CBT + MIT)					
DS	33.5%				
Hall *et al.* (1998) (plus CBT)					
DS					44.9%
NDS					45.1%
Hayford *et al.* (1999)					
DS		37.3%			
NDS		37.2%			

Abbreviations: DS, depressed smokers; NDS, nondepressed smokers; CBT, cognitive behavioral treatment; MIT, motivational interviewing treatment.

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