# A Review of Impact of Tobacco Use on Patients with Co-occurring Psychiatric Disorders

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**ABSTRACT:** Consumption of tobacco has been a worldwide problem over the past few decades due to the highly prevalent tobacco-attributable complications. Tobacco use has also been found to be more prevalent in patients with psychiatric disorders. Therefore, we conducted this review about the impact of tobacco use on co-occurring psychiatric disorders. Various facets of this interaction between tobacco use among those with co-occurring psychiatric disorders have been explored. It has been found that people with psychiatric disorders have a higher chance of currently smoking tobacco and lesser chance of cessation. Tobacco use and mental disorders continue to share a complex relationship that has been further evolving after the change in the pattern of tobacco use and also the advent of newer modalities of treatment. However, at the same time, it is believed that cessation of smoking may lead to improvement in the symptoms of mental illness.

**KEYWORDS:** tobacco, mental illness, dual diagnosis, dual disorders, psychiatric disorders, comorbidity

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## Introduction

Consumption of tobacco has been a worldwide problem over the past few decades due to the highly prevalent tobacco-attributable complications. It is known to be associated with respiratory diseases, cardiovascular diseases, gastrointestinal diseases, and diseases of the urogenital tract and is also implicated for a number of malignancies. According to the estimates of the World Health Organization, tobacco use in any form causes about six million deaths globally, and one-fifth of them occur in the Southeast Asian region alone.[1] In India itself, smoking tobacco was attributed to 0.9 million deaths in a year,[2] whereas another 0.35 million deaths were due to smokeless tobacco.[3]

Tobacco use has also been found to be more prevalent in patients with psychiatric disorders. It has been found that people with psychiatric disorders have a higher chance of currently smoking tobacco and lesser chance of cessation.[4,5] The severity of smoking increases with higher number of co-occurring disorders.[4] The pattern of tobacco use also depends on the type of co-occurring psychiatric disorder. On the contrary, evidence also states that people who smoke have a higher chance of meeting the criteria for several psychiatric disorders.[6,7]

Tobacco use and psychiatric disorders continue to share a complex relationship that has been further evolving after the change in the pattern of tobacco use and also the advent of newer modalities of treatment. However, at the same time, it is believed that cessation of smoking may lead to improvement in the symptoms of psychiatric illness.[8] Therefore, we conducted this review about the impact of tobacco use on co-occurring psychiatric disorders. Our review tried to address the following research questions:

a) What is the prevalence of nicotine dependence in patients with psychiatric disorders?
b) What is the effect of nicotine use in patients with psychiatric disorders?
c) What is the nature of interaction between nicotine and psychotropic medication?

## Methods

A search was conducted on PubMed using the following search terms: "tobacco," "nicotine," "dependence," "tobacco use disorders," "nicotine use disorder," "nicotine abuse," "tobacco abuse," "addiction," "mental illness," "mental disorders," "schizophrenia," "psychosis," "psychotic disorders," "bipolar affective disorders," "anxiety disorders," "mood disorders," "depression," "substance use disorders," "adolescent," "ADHD," "conduct disorders," "psychopharmacology," "management," "alcohol use disorders," "cannabis use disorder," and "opioid use disorders." We selected the studies published between 2000 and 2015. A secondary search was conducted among the references of the studies, and studies on specific themes were accessed.

**Study selection.** The studies that were included in the current review dealt with the impact of tobacco use on patients with co-occurring psychiatric disorders. For the sake of brevity, the authors decided that the scope of psychiatric disorders will include schizophrenia and other psychotic disorders, bipolar affective disorder (BPAD), depressive disorders, anxiety disorders, and attention deficit hyperactivity disorder (ADHD). No limitations were placed regarding the methodological designs of the studies. The abstracts of the studies were initially screened and full texts of the selected studies were accessed. Only articles whose full text could be accessed and were in English language were included in this review. Both the authors were involved in the selection and verification of the studies. Overall, 60 papers were selected within a designated time frame.

## Epidemiology

According to the World Health Organization, tobacco in any form is used by about 1.2 billion people worldwide. In India, tobacco was found to be prevalent among 55.8% respondents in a nationwide survey (National Household Survey of Drug and Alcohol Abuse).[9] It has also been found that the rates of tobacco use are higher in patients with psychiatric disorders. In the Epidemiological Catchment Area study, it was found that 29% of people suffering from psychiatric disorders had a comorbid substance use disorder as compared to 13% among people without any mental disorder.[10]

If we explore the link of tobacco use with the individual disorders, a similar picture can be seen. It has been shown that people with schizophrenia have about five times higher chances of being found currently smoking than the general population.[11] The prevalence of tobacco use has been found to be persistently higher in patients with BPAD than that in the general population. The results have been supported by studies done in the general population[12] as well as in the nonrepresentative clinical population.[13] Tobacco smoking and depression seem to have a bidirectional relationship. Smoking has been found to be more prevalent in patients with depression. About one-third of patients with depression reported of current tobacco smoking.[14] In addition, about 60% of patients with a current diagnosis or past history of depression were found to be smoking either currently or in the past.[12] On the other hand, people who are dependent on tobacco are more likely to suffer from a depressive episode as compared with nonsmokers.[15] The prevalence of tobacco dependence is also found to be higher in patients with anxiety disorders than that in the general population.[16] Studies have also shown that the prevalence of anxiety disorders in smokers is also higher than that in the general population and the trend has been on an increase.[17] Though the data have been found to be heterogeneous for proper comparison, smoking has been found to be consistently related to the increase in the prevalence of panic disorder and generalized anxiety disorder.[18] The prevalence of smoking in patients with ADHDs has been found to be higher than that in the normal controls. The results show that it is 1.5 times more common in adults and about two times more common in adolescents with ADHD.[19–21]

## Interaction of Nicotine Dependence with Co-occurring Psychiatric Disorders

Nicotine dependence is known to play a very complex role in other co-occurring psychiatric disorders. In the subsequent sections, we will address the interface of nicotine dependence and the major psychiatric disorders.

**Schizophrenia and other psychotic disorders.** It has already been mentioned that patients with schizophrenia have a higher rate of smoking and their chances of being able to give up smoking are also bleaker than those of the general population.[11] In addition, patients with schizophrenia who smoke also tend to have a greater habit size and tend to extract more nicotine from each cigarette.[22] Schizophrenia has also been proven to carry a higher mortality and morbidity rate. One of the major contributing factors to it was found to be nicotine dependence. Nicotine dependence is postulated to cause schizophrenia by contributing to the causation of various malignancies and also worsening the physical status and quality of life by causing various cardiovascular, respiratory, and metabolic diseases.[23] Though nicotine use on a short-term basis is known to improve the cognitive abilities,[24] current smoking was also found to be more associated with worse cognitive outcome and poorer functioning in patients with schizophrenia than that among the general population on a longer term.[24]

There are mainly two hypotheses regarding the higher prevalence of nicotine use in patients with schizophrenia. One is the self-medication hypothesis that states that the patients with schizophrenia smoke more in order to deal with the distress arising out of their symptoms. The other is called the addiction vulnerability hypothesis that proposes that the two illnesses co-occur due to the shared genetic and neurodevelopmental abnormalities.[25]

Various authors have also conceptualized the deficiencies present in schizophrenia and nicotine dependence to be sharing its neurobiology, as both have shown abnormalities in the dopaminergic and cholinergic transmission in the mesolimbic areas. Schizophrenia is known to be associated with abnormalities of the P50 gating mechanism. This is implicated in the inability of the patient with schizophrenia to separate the irrelevant distracting noises from the relevant necessary auditory perception. This abnormality has also been considered to be one of the causes of auditory hallucination. Nicotine use has been shown to temporarily correct this abnormality.[26] Another important finding is that the P50 gating abnormalities have also been found to be associated with a smaller hippocampal volume and a decrease in the density of $\alpha 7$ receptors in the brain. Further studies looking at the chromosomal abnormality associated with the P50 gating abnormality tracked it to chromosome 15q13-14, which is also the location of the $\alpha 7$ nicotinic acetylcholine receptors (nAChRs).[27,28]

In the same way, recent research has also focused on the role of other genes, such as BDNF Val66Met polymorphism,[29] and peripheral DISC1 protein.[30] BDNF Val66Met polymorphism was found to be correlated with the severity of nicotine use, whereas peripheral DISC1 protein was found to be a probable candidate for monitoring the severity of the effects of nicotine dependence.

**Bipolar affective disorder.** Tobacco use in patients with BPAD was found to be more likely to contribute significantly to mortality. A retrospective evaluation of tobacco-related deaths in patients with severe mental illness over 15 years found that about 48% of the deaths could be attributed to tobacco.[31] A study that tried to find out the correlates of heavy smoking among adolescents with BPAD and cannabis use disorder found nicotine dependence to be highly prevalent and significantly correlated with White race, severe mania, and poor functioning.[32]

We are still in considerable darkness regarding the relationship of BPAD and smoking. One of the theories put forward is that the symptoms of BPAD can lead to initiation as well as increase in smoking. Tobacco smoke is known to have monoamine oxidase inhibitory effects,[33] which leads to improvement in mood. On the other hand, nicotine is also known to activate the well-known reward circuits. As a result, smoking is known to have a mood-elevating effect and can contribute in the initiation and maintenance of tobacco smoking. Another postulation opines that smoking may lead to unmasking of the latent inherent predispositions of developing BPAD. This theory gathers further support from the evidence that nicotine use may lead to depression by decreasing the number of nAChRs in the limbic system.[34] Evidence is also present to show that long-term smokers who suddenly stop smoking can be predisposed to low mood due to its action on the serotonergic receptors in the hippocampal region.[35] There is also evidence that shows that current smoking with BPAD has a worse cognitive performance and may also play an important role in the patients' decision-making regarding continuation and cessation of smoking.[26] Furthermore, it has also been seen that there is a significant gender difference in decision-making regarding tobacco use with females who are likely to rely on more external causes to give up on smoking.[36]

BPAD and smoking also share a few candidate genes. They include genes that encode for catechol-*O*-methyltransferase, the dopamine transporter and the serotonin transporter.[37] Another attempt was made to look whether BPAD modifies the relationship of nicotine dependence with the β3 nAChRs subunit gene, but it led to a negative result.[38] Another study also managed to find out that patients with BPAD with reduced hippocampal glutathione assessed by proton magnetic resonance spectroscopy (MRS) were associated with severer nicotine use.[39]

**Depressive disorders.** Depression is found to be one of the major causes of initiation of tobacco smoking.[40] It is also a risk factor for a larger habit size and a shorter time to the first cigarette of the day.[41] Tobacco also complicates illness presentation by causing an increase in the risk of suicide in patients with depression.[42]

Some studies also managed to suggest a genetic link between nicotine dependence and depression, with a few implicating both a dose–response association and a shared genetic liability behind the relationship between nicotine dependence and depression.[43,44] Another longitudinal study using a representative community sample of same-sex twins found that neither of the two disorders had a predominant influencing effect on the other.[45] This shared genetic liability along with the clinical observation of the close relationship between depression and nicotine dependence led to the use of antidepressants in the treatment of nicotine dependence.

**Anxiety disorders.** It has already been stated that patients with anxiety disorder have a higher prevalence of tobacco use and vice versa. To add to that, it has also been found that patients with anxiety disorders become dependent on nicotine after smoking lesser number of cigarettes as compared to the normal population.[46]

There is a dearth of literature exploring the relationship between nicotine dependence and anxiety disorders. However, most of the available literature points to a multifactorial relationship. For example, studies have found that there is a sequential role of negative effect on patients with anxiety disorder, which predisposes the patient to smoke in order to deal with it.[47,48] On the other hand, other studies have also implicated factors in the personality setup of the patient such as the presence of cognitive vulnerability that may contribute to the continuation of smoking.[49]

However, there has been reasonably robust evidence of the neurobiological aspect of the relationship of nicotine dependence with anxiety disorder. It has been observed that stressful situations result in pulsatile release of cortisol, which has also been found to be responsive to administration and deprivation of nicotine.[50] It has also been observed that posttraumatic stress disorders (PTSDs) also cause alterations in the hypothalamic–pituitary axis (HPA), which may increase the risk of nicotine dependence.[51] This modulation of the HPA by stress and its responsiveness to nicotine are also known to have a complex interplay, where the genetic, environmental, and neurobiological factors are known to play a role.

**Attention deficit hyperactivity disorder.** A large-scale study[52] involving a sample of around 15,000 adolescents found a positive correlation between the severity of symptoms of ADHD, the lifetime risk of developing nicotine dependence, and the number of cigarettes smoked per day and an inverse relationship with the age of initiation of smoking.

Both the disorders also share a common neurobiological basis after studies were able to find out similar genetic markers.[53] Another important finding that has been observed in patients with ADHD is the dysfunctional dopaminergic system in the corticostriatal tracts, which has also been implicated in the higher chances for the development of nicotine dependence.[54]

**Effect of tobacco cessation on the course of psychiatric illnesses.** One of the major reasons of interest on smoking cessation in patients with psychiatric illness was to see the effect of smoking cessation on the course of the illness. However, studies in this field have been lacking, despite the promise. Researchers have been trying to understand the complex relationship between smoking cessation and its effect on the course of schizophrenia. Though a satisfactory answer is still being awaited, it has been seen that reduction in smoking improves the physical status of the patients and could increase the motivation to quit smoking.[55,56]

We could not access any study addressing the effect of tobacco cessation in patients with BPAD. However, there are more studies addressing this issue in case of patients with depressive disorders or anxiety disorders. In a meta-analysis involving 26 studies on subjects assessed on scales for evaluating symptoms of anxiety disorders, depression, and mixed anxiety and depression, which included follow-ups between seven weeks and nine years, patients who were able to give up smoking had a better psychological quality of life and positive effect.[57] This effect size was equal for subjects with and without psychiatric illnesses.

## Treatment of Nicotine Dependence in Patients with Co-occurring Psychiatric Disorders

Nicotine dependence is often overlooked during the management of various psychiatric illnesses; however, attempts to treat nicotine dependence often become frustrating due to the complex interactions of the two disorders. Here, we review the evidence of treatment of nicotine dependence in patients with co-occurring psychiatric disorders.

**Schizophrenia and other psychotic disorders.** Due to the high prevalence of tobacco use in patients with schizophrenia, there has been a continuous interest in finding out effective treatment modalities. However, despite this fact, we are still far from a confident answer to the problem. Among the various options available such as pharmacotherapy, bupropion has been shown to have the best potential.[58]

A recent Cochrane review[28] analyzed the benefits and harms of different treatment modalities of nicotine dependence in patients with schizophrenia. It included 21 randomized trials and a meta-analysis of various treatment modalities. Bupropion was found to have a robust evidence of being able to decrease the habit size of tobacco use in patients with schizophrenia, but without any improvement or worsening in the positive, negative, or depressive symptoms of schizophrenia. The only other modality that had some evidence was contingent reinforcement with money. Thus, options such as nicotine replacement therapy (NRT) and varenicline were found to have no evidence in the treatment of nicotine dependence in patients with schizophrenia, though it should be said that there were very few studies that were included. However, other evidence suggests that there are higher chances of being abstinent from nicotine when bupropion or NRT is added to the antipsychotics as compared to the antipsychotics alone.[59,60] Varenicline has some evidence to show improvement in the chances of abstaining from tobacco[61] and also improvement in the cognitive abilities.[62] However, there are case reports of varenicline causing exacerbation of psychotic symptoms in patients with schizophrenia.[63] The Cochrane review[28] also had included a few studies that had subjected the patients to behavioral therapies along with pharmacotherapy, but none of those studies directly compared the effects of the two disorders.

Due to the effect nicotine has on the metabolism of the drug, another important issue that needs to be raised is the appropriate choice of antipsychotic and its proper dosing.

**Bipolar affective disorder.** Patients with BPAD were also found to be highly unreliable about reporting their nicotine use even while they were in remission[64] and were also found to be unaware of the risk involved with tobacco smoking and had poor readiness to quit.[65] Pharmacological treatment of nicotine dependence involves certain amount of caution due to the obvious risk posed by the antidepressant property of bupropion.[66] Besides, there are also case reports of manic episodes associated with the use of varenicline[67] and NRT.[68]

**Depressive disorders.** As already mentioned, bupropion remains the only antidepressant that has been approved by the US Food and Drug Administration for the treatment of nicotine dependence. There is insufficient evidence suggesting any particular pharmacotherapy having superior benefit than others in treating comorbid depression and nicotine dependence. However, there has been considerable evidence regarding the benefit of adding cognitive behavioral therapy that targets both the mood symptoms and nicotine use.[69]

**Anxiety disorders.** Data regarding the best way to treat nicotine dependence in patients with anxiety disorder are surprisingly scarce, given the high prevalence of their comorbid existence. However, the best evidence exists for bupropion[70] from a double-blind placebo-controlled study done on patients with PTSDs. The role of the nonpharmacological methods continues to remain important, with the newer modes such as mobile contingency managements also gaining evidence.[71]

**Attention deficit hyperactivity disorder.** Bupropion is considered to be the most promising treatment option for nicotine dependence in ADHD, considering its success in treating adult patients with ADHD.[72] However, there is dearth of enough research about the role of other pharmacological options in treating comorbid ADHD and nicotine dependence. Nonpharmacological approaches such as cognitive behavioral therapy are considered to be useful adjunct treatment options to the existing regime, especially when it is targeted against both nicotine dependence and ADHD.

## Interaction Between Smoking and Psychotropic Medication

**Impact of smoking on psychiatric medication.** Using nicotine has also been shown to have a profound effect on the metabolism of psychotropic medications. Nicotine is

**Table 1.** Psychotropic drugs that are substrate for CYP1A2 and CYP2A6.

| PSYCHOTROPIC DRUGS METABOLIZED BY CYP1A2 | PSYCHOTROPIC DRUGS METABOLIZED BY CYP2A6 |
|---|---|
| Clozapine | Amitriptyline |
| Fluvoxamine | Clomipramine |
| Imipramine | Codeine |
| Olanzapine | Desipramine |
| Pimozide | Imipramine |
| Propranolol | Nortriptyline |
| | Oxycodone |
| | Paroxetine |
| | Risperidone |
| | Thioridazine |
| | Tramadol |
| | Venlafaxine |

primarily metabolized by cytochrome P1A2 (CYP1A2) and cytochrome P2A6 (CYP2A6). Thus, when a patient starts smoking while on being psychotropic medications, it leads to induction of these enzymes and thus causes a decrease in their serum level. In the same way, smoking affects the action of a number of psychotropic medications, such as diazepam, haloperidol, olanzapine, clozapine, and mirtazapine, which are metabolized by CYP1A2.[73] Similarly, care is also required when the patient opts for smoking cessation, as the serological levels of the drugs are expected to rise at that time.

Table 1 summarizes the psychotropic substances that act as substrates of the isoenzyme cytochrome P450.

**Impact of psychotropic medications on smoking.** It has been already mentioned that smoking is often inherently related to the patients' attempt to deal with the negative affective state associated with the various disorders mentioned earlier. Another interesting observation has been the differential status of the smoking habit size when the patient is initiated on different antipsychotics. It has been found that patients on first-generation antipsychotics, such as haloperidol, tend to smoke more as compared to those on second-generation antipsychotics, such as olanzapine or risperidone. This difference is attributed to the increased activities in the dopaminergic and glutaminergic tracts in the cortical regions.[74]

## Conclusion

It has been established that nicotine dependence is highly prevalent among the various mental disorders. However, in spite of this high rate of co-occurrence, the diagnosis and treatment of nicotine dependence continues to be neglected among those with co-occurring psychiatric disorders. Though treatment options available for primary nicotine dependence are expected to remain valid in the co-occurring conditions, further research is necessary to address the issue of poor response to treatment. Our review consists of only those studies whose full text could be accessed. However, in spite of this limitation, we recommend that it is necessary and of utmost importance to reinforce the evaluation of tobacco use in every person with a psychiatric disorder and to offer appropriate intervention. This will decrease the adverse physical effects of smoking and also improve the outcome of treatment of the comorbid mental disorders.

## Author Contributions

Conceived and designed the experiments: AP and YPSB. Analyzed the data: AP and YPSB. Wrote the first draft of the manuscript: AP and YPSB. Contributed to the writing of the manuscript: AP and YPSB. Agree with manuscript results and conclusions: AP and YPSB. Jointly developed the structure and arguments for the paper: AP and YPSB. Made critical revisions and approved final version: AP and YPSB. Both authors reviewed and approved of the final manuscript.

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