Co-Morbidity of Smoking in Patients with Psychiatric and Substance Use Disorders

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Abstract

This article reviews cigarette smoking in patients with psychiatric disorders (PD) and substance use disorders (SUD). Rates of smoking are approximately 23% in the U.S. population but approximately two- to four-fold higher in patients with PD and SUD. Many remaining smokers have had repeated smoking cessation failures, possibly due to the presence of co-morbid PD and SUDs. There is modest, evidence-based support for effective treatment interventions for nicotine addiction in PD and SUD. Further research is needed to increase our understanding of nicotine addiction in PD and SUD and develop more effective treatment interventions.

Although smoking prevalence in the United States has decreased from 43.8% in 1965 to 23.3% in 2000,[1] there are many cigarette smokers who have been unable to quit. An important subset of refractory smokers are those with psychiatric disorders (PD) and substance use disorders (SUD), among whom smoking rates exceed those in the general population by two- to fourfold.[2] In a population-based study of smoking prevalence in the U.S., Lasser and colleagues found that smoking prevalence among persons with and without a psychiatric disorder were 41% and 22.5%, respectively.[2] The highest prevalence (67.9%) was found among persons with drug abuse. Consistent with these results, Degenhardt and Hall[3] reported similar findings in their study of smoking prevalence in Australia. The prevalence of smoking in various PD and SUD[4] is presented in Fig. 1. Other studies have found that individuals with PD and SUD are at higher risk for many tobacco-related diseases, including cardiovascular illness, respiratory disease, and cancer, than individuals in the general population.[5–8]

Among "ever smokers," persons with PD or SUD are less likely to be former smokers than other smokers. Lasser et al.[2] found that the quit rate among ever smokers with no history of PD or SUD was 42.5%. Significantly lower quit rates were associated with several other PD and SUD, including alcohol use disorder (16.9%), bipolar disorder (25.9%), major depression (26.0%), and post-traumatic stress disorder (23.2%). Clearly, improved treatments for nicotine addiction are needed for these populations.

Several explanations have been proposed for the high prevalence of smoking in individuals with PD and SUD. First, there may be intrinsic factors (eg, shared genes, abnormalities in brain

reward pathways) that predispose individuals with PD and SUD to smoking. Second, nicotine may be used by PD and SUD patients to self-medicate psychiatric symptoms.[9–12] Accordingly, concurrent presentation of PD and SUD (eg, "dual diagnosis") is often associated with cigarette smoking.[13] Furthermore, nicotine administration through cigarette smoking may modulate several neurotransmitter systems (eg, dopamine, glutamate) thought to be involved in the pathogenesis of PD and SUD.

This article reviews the existing literature on cigarette smoking in individuals with PD and SUD, with reference to neurobiology, clinical findings, and treatment approaches for smoking cessation in these populations. Recommendations for the treatment of nicotine addiction in these populations are also discussed, and gaps in our current knowledge are identified.

NEUROBIOLOGY

Neuropharmacology

Nicotine modulates several neurotransmitter systems that are involved in the pathogenesis of PD and SUD, including dopamine (DA).[4,9,14] the reinforcing effects of nicotine are primarily mediated through the activation of nicotinic acetylcholine receptors (nAChRs), located pre-synaptically on mesolimbic DA neurons.[15,16] The role of mesolimbic DA neurons in mediating the reinforcing effects of nicotine is suggested by rodent studies demonstrating that lesions of the VTA reduce nicotine self-administration, as do local infusions of the nAChR antagonist mecamylamine into the VTA.[17,18] It has also been observed that nicotine withdrawal leads to reductions in central DA in rodents[19,20] and urinary catecholamine excretion in human smokers.[21,22]

Nicotine facilitates the release of other neurotransmitters, including acetylcholine (ACh), endogenous opioid peptides (EOPs), γ-aminobutyric acid (GABA), glutamate (Glu), norepinephrine (NE), and serotonin (5-HT), which are also involved in the pathogenesis of PD and SUD.[16] These biochemical and pharmacological findings provide a conceptual link between cigarette smoking and putative neurobiological abnormalities underlying several PD and SUD. A summary of the neurotransmitter systems that may contribute to the higher rates of smoking in PD and SUDs is given in Table 1.

Genetics

Few studies have evaluated genetic factors as determinants of the high co-morbid rates of smoking in PD and SUD. Kendler and colleagues[23] examined 1566 female twin pairs from the Virginia Twin Registry using a best-fitting bivariate twin model and found evidence for shared genetic factors to explain the association between smoking and major depression. Another study of 173 monozygotic and 183 dizygotic male twin pairs from the National Heart Lung and Blood Institute's Twin Study suggested that the heritability of smoking may relate to common factors determining substance abuse.[24]

The genetic influence of alleles of several post-synaptic DA receptors (D_1, D_2, and D_4) and the dopamine transporter (DAT), which have been studied as genetic determinants of PD and SUD (eg, schizophrenia and cocaine dependence), have been implicated in cigarette smoking behavior. D1 dopamine receptor (D1DR) alleles[25] and D2DR gene polymorphisms[26,27] have been associated with differences in smoking behavior, and polymorphisms in the D4DR gene have been associated with smoking and depression.[28] In addition, polymorphisms in the DAT have been associated with lower rates of smoking and longer periods of smoking abstinence.[29]

Genetic variations in nAChRs and the enzymes involved in nicotine metabolism in PD and SUD may explain high rates of smoking in these disorders. For example, Freedman and

colleagues[30] have found evidence for an allelic variation in the α7 nAChR subunit gene in schizophrenic patients associated with auditory gating deficits, which may explain their high rates of smoking. The primary hepatic enzyme system involved in the metabolism of nicotine to cotinine is CYP 2A6. Recent work by Tyndale and colleagues[31] suggests that individuals with one or more null alleles (that do not lead to active enzyme products) of the CYP 2A6 hepatic microsomal system smoke significantly fewer cigarettes per week, and smokers with such null genotypes have reduced expired breath carbon monoxide and plasma cotinine levels. [32] However, there have been no studies describing abnormalities of CYP 2A6 expression or differences in the presence of null alleles in patients with PD or SUD as compared to controls. Interestingly, there is evidence that polymorphisms in CYP 2D6 can determine smoking cessation responses to bupropion SR,[33,34] and thus allelic variations in candidate genes related to smoking in PDs and SUDs may have pharmacogenetic treatment implications.

SMOKING AND PSYCHIATRIC DISORDERS (PD)

While higher rates of smoking in patients with PD have been well-described, most published studies of PD have not addressed the role of nicotine and tobacco use as a confounding variable on study outcomes.[35] The failure to account for co-morbid smoking in these studies is an important issue to consider in interpreting such study results. For example, most studies do not control for time of last cigarette, which could create potential artifacts in outcome measures due to varying levels of withdrawal or the misinterpretation of withdrawal symptoms from nicotine as being due to mental illness.

Hypotheses accounting for the high rates of smoking in PD[9,36] include:

1. shared genetic factors that determine vulnerability to both smoking and PD

2. self-medication by cigarette smoking of clinical symptoms, medication side effects, and cognitive deficits associated with PD

3. common environmental factors such as stress that can increase expression of smoking behavior and the onset of psychiatric symptoms.

An overview of relevant clinical studies relating smoking with a number of PD is presented in this section.

Schizophrenia

Patients with schizophrenia have higher rates of smoking (45–88%) compared to the general population in both clinical[4,37] and population-based[2] samples. In clinical samples, smoking rates are higher in inpatient (81.5%)[38–41] compared to outpatient (68.4%)[10,42–49] settings, which is consistent with higher smoking rates in institutional settings. A preliminary report found high smoking rates (92%) in first-episode schizophrenic patients with no history of using anti-psychotic medications. These findings suggest that smoking in this population is related to pathophysiological features of the illness and not to an iatrogenic effect of antipsychotic treatment (eg, an effort to alleviate side effects of medication by smoking).[48] The temporal sequence of smoking preceding the onset of psychotic symptoms is unlikely to suggest a causal connection between smoking and the onset of schizophrenias because a large percentage patients with schizophrenia are *non-smokers* (8–42%), based on clinic-based smoking prevalence surveys,[4] and smoking cessation in schizophrenics does not appear to lead to significant changes (either a worsening or improvement) in psychotic symptoms.[50–52]

Cross-sectional studies have examined the associations between cigarette smoking and psychotic symptoms in patients with schizophrenia.[42,49,53] Goff and colleagues[42] found that schizophrenic smokers had higher Brief Psychiatric Rating Scale (BPRS) total scores than non-smokers and higher levels of positive and negative symptoms. Ziedonis and colleagues[49] found

increased positive symptoms but reduced negative symptoms in schizophrenic smokers versus non-smokers. Heavy smokers had the highest positive and lowest negative symptom scores. While their sample was confounded by diagnostic heterogeneity, Hall and colleagues[53] found that chronically mentally ill patients (87% with schizophrenia or schizoaffective disorder) who were former smokers had fewer negative symptoms (on BPRS) than current mentally ill smokers. However, recent controlled laboratory studies of tobacco abstinence,[54,55] along with data from four controlled smoking treatment trials, have found no evidence for significant changes in psychotic symptoms with smoking cessation[50,51,56] or smoking reduction[52] in schizophrenic patients. Thus, controlled prospective studies have not confirmed the effects of smoking on clinical symptoms in schizophrenia as observed in cross-sectional studies. This suggests that other differences (eg, trait factors) between schizophrenic smokers and non-smokers may explain the results from cross-sectional studies.

The most compelling evidence for a pathophysiologically-based vulnerability to smoking in schizophrenic patients relates to well-defined deficits in psychophysiological measures (eg, P50 auditory gating) and neuropsychological performance deficits that appear to be improved or normalized by nicotine administration or cigarette smoking. For example, nicotine and smoking transiently normalize P50 gating and smooth-pursuit eye movement (SPEM) deficits in schizophrenic patients and their first degree relatives,[57–61] which appear to be mediated by deficient neurotransmission through α7 nAChRs.[30,62] In addition, nicotine and smoking have been shown to remediate working memory[55,63,64] and attentional deficits[55,65,66] in schizophrenics.

Cigarette smoking may reduce neuroleptic-induced parkinsonism[67] but worsen symptoms of tardive dyskinesia,[68] but these effects have not been observed in all studies,[42,44,68] probably due to methodological differences. These observations are consistent with nicotine's enhancement of subcortical DA systems, leading to reduced parkinsonism and increased tardive dyskinesia. The transdermal nicotine patch has been shown to reduce bradykinesia associated with haloperidol administration,[69] lending some direct experimental support to the anti-parkinsonian effects of nicotine.

Affective Disorders

Depressive Disorders.—In clinical samples of patients with major depression,[10,11,70,71] and in a population-based sample with clinically significant depressive symptoms,[72] smoking prevalence is 40–60%. Glassman and colleagues[73] found that 61% of smokers presenting to a smoking cessation program in New York City had a past history of major depression. In a clinical sample of 547 Latinos in San Francisco, Perez-Stable and colleagues[74] reported that depressive symptoms (as determined by Center for Community Epidemiological Studies Depression Scale [CES-D] scores >16, suggesting clinically significant depression) were higher in Latino current smokers (21.9% and 39.5% for males and females, respectively) than Latino former (9.8% and 27.0%) and never (11.8% and 18.5%) smokers. Similarly, in a population-based study of depressive symptoms and smoking, Anda et al.[72] found that 39% of individuals with CES-D scores >16 were current smokers. It has also been observed that smokers with depressive symptoms have a much harder time quitting,[73,75] and require more smoking cessation attempts to successfully quit,[76,77] and that smoking cessation is associated with the emergence of negative affective states.[70] For those patients with a history of major depression, smoking cessation may lead to a reemergence of major depressive symptoms,[76,78] though this phenomenon has been questioned.[79,80] Furthermore, Breslau et al.[81] demonstrated that the severity of tobacco withdrawal appears to be worse in individuals with major depression or anxiety disorders.

Bipolar Disorder.—There have been few studies on co-morbid smoking and bipolar disorder[10,82–84] and no studies on the treatment of smoking in this disorder. Hughes and colleagues[10] reported a smoking prevalence of 70% in bipolar patients from Minnesota, while in a Spanish population of chronically mentally ill patients, Gonzalez-Pinto and associates[82] reported that 63% of patients had lifetime histories of smoking and 51% were current smokers, as compared to 33% in the control group. More recent studies[83,84] have found similarly high rates (55–70%) of smoking in bipolar disorder. Corvin and associates[84] found evidence that smoking may be more prevalent with the presence of psychotic symptoms in bipolar disorder, but this finding was not supported in another study.[83] One population-based study suggested that the prevalence of current smoking in bipolar disorder was 60.6% and also found lower quit ratios in bipolar smokers as compared to those without mental illness.[2] It remains to be determined whether the relationship between increased smoking prevalence and reduced success in smoking cessation attempts in patients with bipolar disorder parallel clinical findings observed in unipolar depression, though a study by Glassman and colleagues did find that bipolar patients were at a particular risk for depressive recurrence during smoking cessation. [77]

Anxiety Disorders

Panic Disorder.—Smoking prevalence in panic disorder varies widely across studies, ranging from 19.2% to 56%.[2,85–88] Two longitudinal studies indicate that daily smoking is predictive of the onset of panic attacks, but not vice versa.[89,90] Most recently, a third study prospectively examined the bidirectional relationship between smoking, nicotine dependence (ND), and anxiety disorders in adolescents and young adults.[91] Prior regular smoking and ND were associated with an increased risk for new onset of panic attacks. However, due to discrepancies between the data analytic methods used, the authors could not conclusively rule out the potentially less common pathway of pre-existing panic attacks or disorders influencing the later development of ND. Additional research is needed to explore these pathways, including possible mediators to explain the progression from one disorder to the other and moderators that determine when and whether the progression occurs.

Obsessive-compulsive Disorder (OCD).—The prevalence of smoking among patients with OCD appears to be the lowest among the anxiety disorders (7.7% to 22.4%[85,88,92,93]) and PD in general. Reasons for the lower occurrence of smoking in OCD are unclear but could be related to the specific nature of OCD symptoms (eg, fears of disease, contamination) or a combination of factors, including the effects of nicotine, genetic factors, or the social effects of having OCD.[92]

Post-traumatic Stress Disorder (PTSD).—Prevalence estimates of smoking range from 53–66% in combat veterans with PTSD.[94–96] Smoking prevalence has also been shown to differ based on high (56%) vs. low (39%) combat exposure.[97] The majority of empirical studies on PTSD and smoking have been conducted with combat veterans. Higher rates of heavy smoking (>25 cigarettes/day) have been reported in PTSD versus non-PTSD veterans (48% vs. 28%, respectively[95]). Heavy smokers also report greater levels of total PTSD symptoms and Cluster C (avoidance and numbing) and Cluster D (hyperarousal) symptoms. Other studies have demonstrated that nicotine withdrawal symptoms are worse in smokers with PTSD in response to trauma-related stimuli as compared to those without PTSD.[98]

In women with PTSD related to physical and sexual assault, Acierno et al.[99] found a smoking prevalence of 44.4% (vs. 26.1% in those without PTSD). Recently, Vlahov et al.[100] examined civilian smoking rates and prevalence after the United States terrorist attacks on September 11, 2001. Similar to national smoking levels, 23.4% of participants reported current smoking. Among those who were actively smoking prior to September 11th, 41.2% increased their

smoking. Those who increased their smoking were more likely to report symptoms of PTSD (24.2%) compared to smokers who did not increase their smoking (5.6%).

With respect to trauma exposure and risk of smoking, Anda et al.,[101] controlling for confounding variables such as socioeconomic status and age, found that compared to individuals who never experienced an adverse childhood event, those with a history of five or more adverse events (eg, verbal, physical, or sexual abuse; divorce; a battered mother; substance abuse, mental illness, or an incarcerated household member) had greater risks of early onset smoking (OR: 5.4), ever smoking (OR: 3.1), and heavy smoking (OR: 2.8). Moreover, data from a 10-year prospective study indicated that trauma exposure predicted later development of ND (OR: 1.81) but that the risk of developing ND was significantly greater in those with PTSD (OR: 3.30).[102] When examining retrospective lifetime data, only PTSD, but not trauma-exposure alone, predicted the subsequent development of ND. Collectively, these data suggest that PTSD and perhaps trauma exposure increase the risk for the later development of ND.

Attention-Deficit Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is associated with higher rates and earlier onset of cigarette smoking,[103] which has a pattern of familial transmission. There is evidence that nAChR mechanisms may be involved in the pathophysiology of ADHD, as the high-affinity nAChR agonist ABT-418 may be useful for the treatment of ADHD symptoms.[104]

SMOKING AND SUBSTANCE USE DISORDERS (SUD)

Over 75% of alcohol- and drug-dependent persons in early recovery smoke cigarettes[105–107] and tend to be heavy, highly nicotine-dependent smokers;[108] smoking-related mortality exceeds alcohol-related mortality in this population.[5]

Alcohol Use Disorders

Animal and human studies have suggested that the effects of alcohol consumption are partially mediated by nAChRs and that stimulation of nAChRs may enhance alcohol consumption.[109–111] Le and colleagues[112] demonstrated that exposure to nicotine enhanced alcohol consumption in rats. Blomqvist et al.[110,112] have shown that the high-affinity nAChR antagonist mecamylamine decreased alcohol consumption in high- but not low-alcohol-preferring rats. More recently, Blomqvist et al.[109] demonstrated that mecamylamine versus placebo pretreatment decreased alcohol consumption and the rewarding effects of alcohol in humans with no history of an alcohol, tobacco, or other drug dependence.

Consumption of an alcohol versus a placebo beverage acutely increases smoking behavior.[113] Another study[114] found that smoking acutely increased the reinforcing value of alcohol; however, this effect was observed only following alcohol pre-exposure in men. Moreover, in a population of smokers in alcohol treatment, urges to smoke increased during exposure to alcohol versus water cues,[105,115,116] and urges to smoke and drink were positively correlated during exposure to alcohol cues.[106] These data are consistent with a learning theory explanation of the association between drinking and smoking urges and use; that is, with repeated pairing of these behaviors, smoking urges (and smoking) become a conditioned response to alcohol cues which serve as unconditioned stimuli.

Cocaine

Individuals who use cocaine have high rates (~80%) of co-morbid cigarette smoking.[117,118] Significant reductions in cigarette consumption have been found after cocaine discontinuation.[117] The presence of cigarette smoking in individuals with cocaine dependence

is associated with earlier onset of cocaine use, more severe use, more legal problems, and use by intravenous or smoked routes of administration.[119]

Horger and colleagues[120] found that nicotine potentiates cocaine self-administration in rats, suggesting that the stimulation of nAChRs can enhance the rewarding effects of cocaine. Studies in mice[121] found that pre-treatment with the nAChR antagonist mecamylamine or deletion of the β2 subunit of the high-affinity nAChR with the use of transgenic mice can reduce conditioned place preferences to cocaine but not morphine. In humans with nicotine and cocaine dependence, an acute dose of nicotine enhances cue-induced cocaine craving, [122] while a single pre-treatment dose of the nicotinic receptor antagonist mecamylamine reduces cue-induced cocaine craving.[123] Because nAChRs are present on mesolimbic DA neurons and nAChR stimulation augments DA release and metabolism,[20] the blockade of nAChRs may modify DA responses induced by cocaine administration, thereby altering the reinforcing properties of cocaine. This may have implications for the development of treatments for cocaine addiction based on nAChR systems.

Opioids

Greater than 80% of opioid-dependent patients smoke cigarettes.[118,124–128] The presence of depressive symptoms appears to increase the risk of smoking in methadone-maintained individuals.[126] Increases in methadone dose may lead to increased nicotine craving and cigarette consumption.[128] Conversely, heroin abstinence after detoxification has been associated with increased smoking consumption.[129]

Cannabis

Data from the Australian National Survey of Mental Health and Well-Being (NSMHWB) Study[3] found that the prevalence of cannabis use disorders was 0.8% in never smokers, 1.0% in former smokers, and 6.4% in current smokers, with an adjusted Odds Ratio of 5.00 (95% CI; 3.35–7.45) in current smokers. The lack of additional studies of the co-morbidity between tobacco and marijuana use likely relates to the fact that cannabis is typically used in combination with cigarettes and other drugs of abuse.

SMOKING CESSATION IN PD AND SUD

Treatments for Nicotine Addiction in PD and SUD

The development of effective smoking cessation treatments in PD and SUD may depend on their ability to target pathophysiological aspects of the primary disorder. Examples of treatments that target the pathophysiology of a PD or SUD, and which may also target smoking behavior, include atypical antipsychotics for schizophrenia,[43,50,51,130,131] antidepressants for depressive disorders,[132,133] and naltrexone for alcoholism.[134–136] For example, several studies have suggested that switching treatment-refractory schizophrenics from typical antipsychotic agents to clozapine is associated with a reduction in cigarette smoking,[43,130,131] especially in heavier smokers.[43] Atypical antipsychotics may also enhance smoking cessation rates in combination with a nicotine patch[51] and bupropion[50] in schizophrenic patients. The tricyclic antidepressant nortriptyline appears to be efficacious for smoking cessation in smokers with either a positive or negative history of major depressive disorder (MDD), and the combination of this agent with cognitive-behavioral therapy (CBT) was superior in MDD history-positive smokers,[137] suggesting the potential of treatment-matching strategies in smokers with PD. While widely used for treatment of major depression, serotonin-selective reuptake inhibitors do not appear to be efficacious for smoking cessation,[133] including for smokers with concurrent alcoholism and depressive symptoms[138] or a past history of depression.[139] Nonetheless, antide-pressant therapies for smoking cessation have not been systematically evaluated in currently depressed smokers.

Interventions that combine behavioral and pharmacological treatments for co-morbid smoking and psychiatric symptoms may have considerable promise.[36,37,51,56,71,140] For example, the combination of mood-focused CBT with nicotine gum was superior to that of standard behavioral smoking treatments with nicotine gum for smoking cessation in individuals with a past history of major depression.[141] Data also support the utility of mood-focused CBT programs for smoking cessation in patients with histories of combined major depression and alcohol dependence.[142] Brown and colleagues[143] compared standard CBT for smoking cessation alone and in combination with CBT for depression (CBT-D) in smokers with a past history of major depression. Although no overall differences were found between treatment groups, smokers with recurrent major depression or those who were heavy smokers (>25 cigarettes/day) responded better to CBT-D than standard treatment alone, suggesting that the addition of CBT for depression may be beneficial for this subset of smokers.

Recent clinical trials in smokers with SUD have suggested the benefits of nicotine replacement and intensive psychosocial supports,[127,144–148] although findings indicate that persons in early recovery find it very difficult to quit smoking with long-term quit rates rarely exceeding 12%.[149,150] Given that tricyclic antidepressants and bupropion may have efficacy in the treatment of cocaine and other stimulant dependence,[151] controlled studies of these agents for smoking treatment in SUD populations are also warranted. Guidelines for smoking cessation in individuals with PD and SUD have been proposed.[37,149,150,152,153] Based on the current state of knowledge, a summary of recommendations for smoking cessation treatment in PD and SUD is given in Table 2.

Timing of Smoking Cessation and Duration of Treatment in Co-morbid Smokers

It is unclear at present whether treatment of nicotine addiction in PD and SUD should be provided at the same time as treatments for other disorders (concurrent treatment) or implemented after the initiation and stabilization of the PD/SUD (sequential treatment). The example of smoking cessation in recovering alcoholics illustrates the challenges associated with whether to implement smoking cessation interventions sequentially or concurrently. Several smaller studies have suggested that smoking cessation in clinical trials is not associated with increased alcohol and other drug use among persons in recovery.[150,154–156] However, findings from a recent study of smokers in alcohol recovery suggest that it may be important for some smokers in recovery to delay smoking cessation treatment until they have established several months of sobriety. Joseph and colleagues[157] randomly assigned smokers (N = 499) in alcohol treatment to concurrent or delayed (six months after enrollment) smoking cessation treatment. While smoking cessation outcomes were similar at comparable follow-up assessment points, smokers assigned to delayed treatment had significantly better alcohol outcomes. Further study of this issue is warranted.

Despite evidence that it may be prudent to address treatment of alcohol and smoking sequentially, many alcohol abusers prefer concurrent treatment for their alcohol and nicotine addiction and were confident that they could quit drinking and stop smoking within six months.[158] Furthermore, the fact that a substantial proportion of alcohol- and opioid-dependent patients die of tobacco-related illness[5,159] supports the assertion that smoking cessation services be rendered when these patients present to addiction treatment programs, as this offers a "teachable moment." Thus, it would appear that consideration should be given to addressing these problems concurrently, though in practice this is often done sequentially often due to the lack of coordination of treatments for PD/SUD and smoking. This is clearly an area where more controlled study is needed. Based on the current evidence, we suggest addressing treatment of co-morbid PD/SUD and cigarette smoking in a sequential manner. Careful monitoring of relapse in PD and SUD after achievement of smoking cessation is recommended.

The optimal duration of treatment in co-morbid populations is unknown, and most active trials have not exceeded twelve weeks in both the non-comorbid and comorbid smoking treatment literature. Six-month smoking abstinence rates tend to be poor in patients with PD and SUD compared to smokers without these co-morbid disorders.[36,50,51,160,161] Accordingly, the issue of maintenance treatment with nicotine replacement therapy and/or bupropion SR and behavioral therapies for the goal of smoking relapse prevention warrants consideration in PD and SUD populations,[162] given their low probabilities of achieving long-term smoking abstinence. While long-term use of psychosocial and behavioral therapy support (eg, relapse-prevention therapy) might be recommended for smokers with PD and SUD, it is untested in prospective studies. Thus, there is an urgent need to obtain data on such maintenance regimens on treatment outcomes in co-morbid populations and for reducing smoking-related morbidity and mortality rates, especially in light of managed care constraints on reimbursement for providers of smoking cessation services in most states.

Difficulties with Integration of Smoking Cessation Interventions into Mental Health and Addiction Treatment Settings

Since the Joint Commission on Accreditation of Health Care Organizations mandated smoking bans in accredited facilities in 1992, there is a requirement to create smoke-free environments in treatment settings for individuals with PD and SUD. However, Bobo and colleagues[145] found that only one-third of addiction counselors routinely encouraged their patients to quit smoking, and counselors who smoked themselves rarely tended to give such advice. This is problematic since conventional smoking cessation programs offered to community smokers do not appear to serve the smoking cessation treatment needs of individuals with PD or SUD.[51,150] Modifications of conventional smoking cessation programs for individuals with PD[36,51,56,140,145] and SUD[144–147,163,164] appear to show promise for these populations.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Cigarette smoking is highly co-morbid with PD and SUD. In some cases, specific pathophysiological relationships have emerged. The systematic study of cigarette smoking interactions with PD and SUD promises to further our understanding of the biology and treatment of each of the individual disorders. Identification of these high-risk smokers through careful screening for PD and SUD in treatment settings will allow the implementation of potentially effective interventions directed towards reducing rates of smoking and associated medical sequelae.

There is a critical need for more substantiated research on biological and psychosocial factors that suggest causal connections for co-morbid smoking in these disorders and effective treatments directed toward smoking cessation in individuals with PD and SUD. Specifically, more research is needed on the temporal onset of smoking in PD and SUD, on abnormalities in nAChR systems in PD and SUD, and on whether addressing co-morbid smoking in PD and SUD is best approached by concurrent versus sequential treatment approaches. Advances in the treatment of nicotine dependence in co-morbid smokers depends on several factors. First, as Hughes[107] and Hurt and Patten[165] argue, larger controlled clinical trials are needed to test standard smoking cessation treatments in these populations. Rational decisions regarding whether treatment for this population of smokers needs to be tailored can be made based on these findings. Second, data pertaining to drug use history and/or psychiatric symptoms should be collected in these trials. Third, it will be important to investigate predictor (eg, measures of disinhibition, negative affect), moderator (eg, gender), and mediator (eg, self-medication) variables that are relevant to co-morbid populations of interest. Ultimately, advances in understanding the etiology of co-morbid PD, SUD, and smoking will allow for a more rational development of treatments for nicotine addiction in these individuals.

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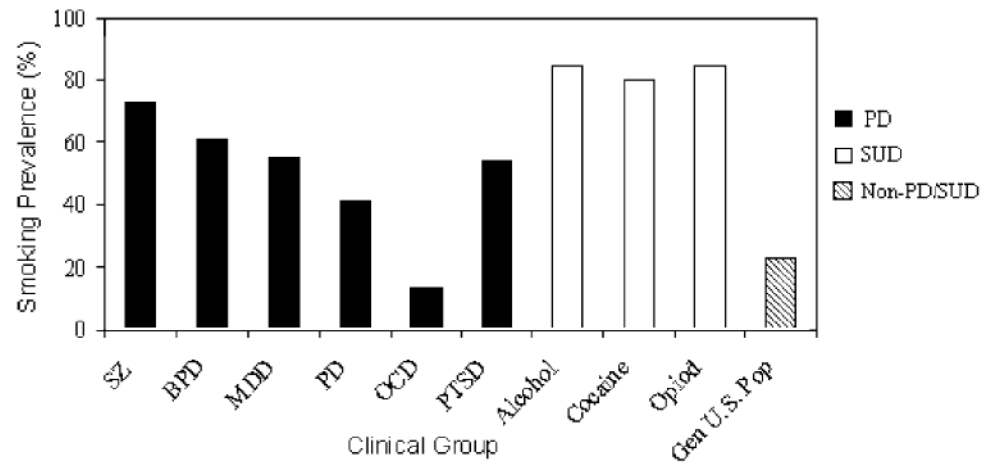
FIGURE 1.
Prevalence of cigarette smoking in clinical samples of individuals with PD and SUD. Data were compiled from clinical studies of smoking prevalence in major PD and SUD.[4] Abbreviations: SZ, schizophrenia; BPD, bipolar disorder; MDD, major depressive disorder; PD, panic disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder.

TABLE 1

Neurotransmitter Systems of Relevance to the Co-Morbidity of Cigarette Smoking in PD and SUD

Neurotransmitter	Brain Region Localization	PD/SUD Involved
Dopamine (DA)	VTA, NAc, SNc, PFC, ACC	Schizophrenia, bipolar disorder, alcohol and drug addiction
Norepinephrine (NE)	LC, PFC	Bipolar disorder, major depressive disorder, cocaine dependence
Serotonin (5-HT)	RN, PFC, OFC	Major depression, PTSD
Acetylcholine (ACh)	NBM, PPN, HIPP, PFC	Schizophrenia, major depression, nicotine dependence
Endogenous opioid peptides (EOPs)	PAG, VTA	Opioid and alcohol dependence
Glutamate	PFC, NAc, VTA, THAL	Schizophrenia, bipolar disorder, major depression
γ-aminobutyric acid (GABA)	PFC, NAc, VTA, THAL	Schizophrenia, major depressive disorder, cocaine dependence
Endocannabinoids (ECBs)	VTA, NAc, HIPP, CEREB	Cannabis and opioid dependence

Abbreviations: VTA, ventral tegemental area; NAc, nucleus accumbens; SN, substantia nigra; PFC, prefrontal cortex; ACC, anterior cingulated cortex; LC, locus ceruleus; RN, raphe nucleus; OFC, orbitofrontal cortex; NBM, nucleus basalis of Meynert; PPN, pedunculopontine nucleus; HIPP, hippocampus; PAG, periaquaductal gray; THAL, thalamus; CEREB, cerebellum.

TABLE 2

Recommendations for the Treatment of Nicotine Dependence in PD and SUD

- Identification of cigarette smoking at each clinic visit

- Assessment of motivation to quit smoking

- Focus on motivating smokers to quit and teaching basic smoking cessation counseling skills to the smoker (eg, motivational interventions, stimulus control, and relapse prevention skills)

- Adjunctive use of combination treatments (eg, NRT plus sustained-release bupropion) in refractory cases of nicotine dependence

- Aggressive treatment of PD and=or SUD first, then treatment of nicotine dependence (sequential treatment)

- Use of pharmacotherapies that target the underlying pathophysiology of the PD=SUD, which constitutes a vulnerability factor for cigarette smoking (eg, atypical antipsychotics in schizophrenia, antidepressants in major depression, naltrexone for alcoholism)