In Review

Mechanisms Underlying the Comorbidity of Tobacco Use in Mental Health and Addictive Disorders

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We discuss potential explanations for the high prevalence of tobacco use and tobacco dependence (TD) in people with mental health and addictive (MHA) disorders. The biopsychosocial basis for this comorbidity is presented, integrating evidence from epidemiologic and clinical studies. We also review evidence that suggests a shared vulnerability related to biological, genetic, and environmental factors may be the most parsimonious mechanism to explain the association between TD and MHA disorders. Finally, we review the examples of various MHA disorders that are associated with TD, and suggest avenues for new investigation that could aid in the development of rationale and more effective treatments for tobacco and MHA disorder comorbidities.

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Highlights

- The prevalence of tobacco use in people with MHA disorders is 2 to 4 times higher than in the general population.
- Reasons to explain the high rates of this comorbidity include the self-medication hypothesis, the shared vulnerability hypothesis, and the social determinants hypothesis. Most of the evidence supports the latter 2 hypotheses.
- Converging genetic, epidemiologic, neuroimaging, neurocognitive, and clinical data suggest that intrinsic features of MHA may predispose to the initiation and maintenance of smoking behaviours in these populations, with the best data available for schizophrenia, mood disorders, and alcoholism.
- A better understanding of the biopsychosocial determinants of tobacco use and MHA comorbidity may lead to the development of more rational, safe, and effective pharmacological and behavioural treatments for this comorbidity.

Key Words: *tobacco, nicotine, mental illness, mechanisms, comorbidity, psychiatric disorders, substance use disorders, treatment, epidemiology*

Although cigarette smoking prevalence in Canada has decreased to about 19%,[1] many smokers are unable to quit. An important subset of these refractory smokers are those with MHA disorders, among whom smoking rates exceed those in the general population by 2- to 4-fold.[2,3] In a population-based study in the United States, Lasser et al[2] found that smoking prevalence among people with and without a psychiatric disorder were 41% and 22.5%, respectively. The highest prevalence of tobacco smoking (67.9%) was found among people with addictive disorders. Moreover, Grant et al[4] found that while nicotine-dependent smokers with mental illness constituted 7.1% of the smoking population, they consumed 34.1% of cigarettes sold. Other studies have found that people with MHA disorders are at higher risk for developing many tobacco-related diseases, including cardiovascular and respiratory disease, and various cancers, compared with the general population.[5–7] Moreover, tobacco-related medical illness may be the leading cause of mortality in MHA smokers.[7,8]

In the Lasser et al study,[2] cessation rates among smokers with no history of MHA disorders was 42.5%. Lower cessation rates were associated with alcohol use disorder (16.9%), nonaffective psychosis (27.2%), BD (25.9%), MDD

(26.0%), and PTSD (23.2%). A summary of smoking prevalence in clinic-based studies is presented in Figure 1. Thus improved treatments for tobacco addiction are needed for these populations and it is likely that better mechanistic explanations for these comorbid associations could assist in the development of novel and improved treatments for this comorbidity.

Several explanations have been proposed for the high prevalence of smoking in people with MHA disorders.[9] First, there may be intrinsic factors (for example, shared genes) that predispose people with MHA to initiation and maintenance of smoking behaviours. Second, nicotine may be used by MHA patients to self-medicate psychiatric symptoms and psychotropic drug side effects.[10–13] Third, there may be common social and environmental determinants of this comorbidity (for example, easy access and availability, poverty, and stressful environments). Not surprisingly, concomitant presentation of MHA disorders (for example, concurrent disorders) is strongly associated with cigarette smoking.[14] Further, nicotine administration through cigarette smoking may modulate several neurotransmitter systems (for example, DA, Glu, and GABA) thought to be involved in the pathogenesis of MHA disorders.

Abbreviations used in this article

ACE	adverse childhood event
ADHD	attention-deficit hyperactivity disorder
AS	anxiety sensitivity
BD	bipolar disorder
CES-D	Center for Community Epidemiologic Studies Depression Scale
CYP	cytochrome P_{450}
DA	dopamine
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
Glu	glutamate
MAO	monoamine oxidase
MDD	major depressive disorder
MEC	mecamylamine
MHA	mental health and addictive
MRI	magnetic resonance imaging
nAChR	nicotinic acetylcholine receptor
OCD	obsessive–compulsive disorder
PET	positron emission tomography
PTSD	posttraumatic stress disorder
TD	tobacco dependence
VTA	ventral tegmental area

We review the existing literature on mechanisms that could explain the comorbidity of cigarette smoking in people with MHA, with reference to biobehavioural and psychosocial determinants of this comorbidity. Based on this knowledge, recommendations for further research in MHA populations are proposed.

Biobehavioural Explanations for the Higher Prevalence of Tobacco Use in MHA

Neuropharmacological

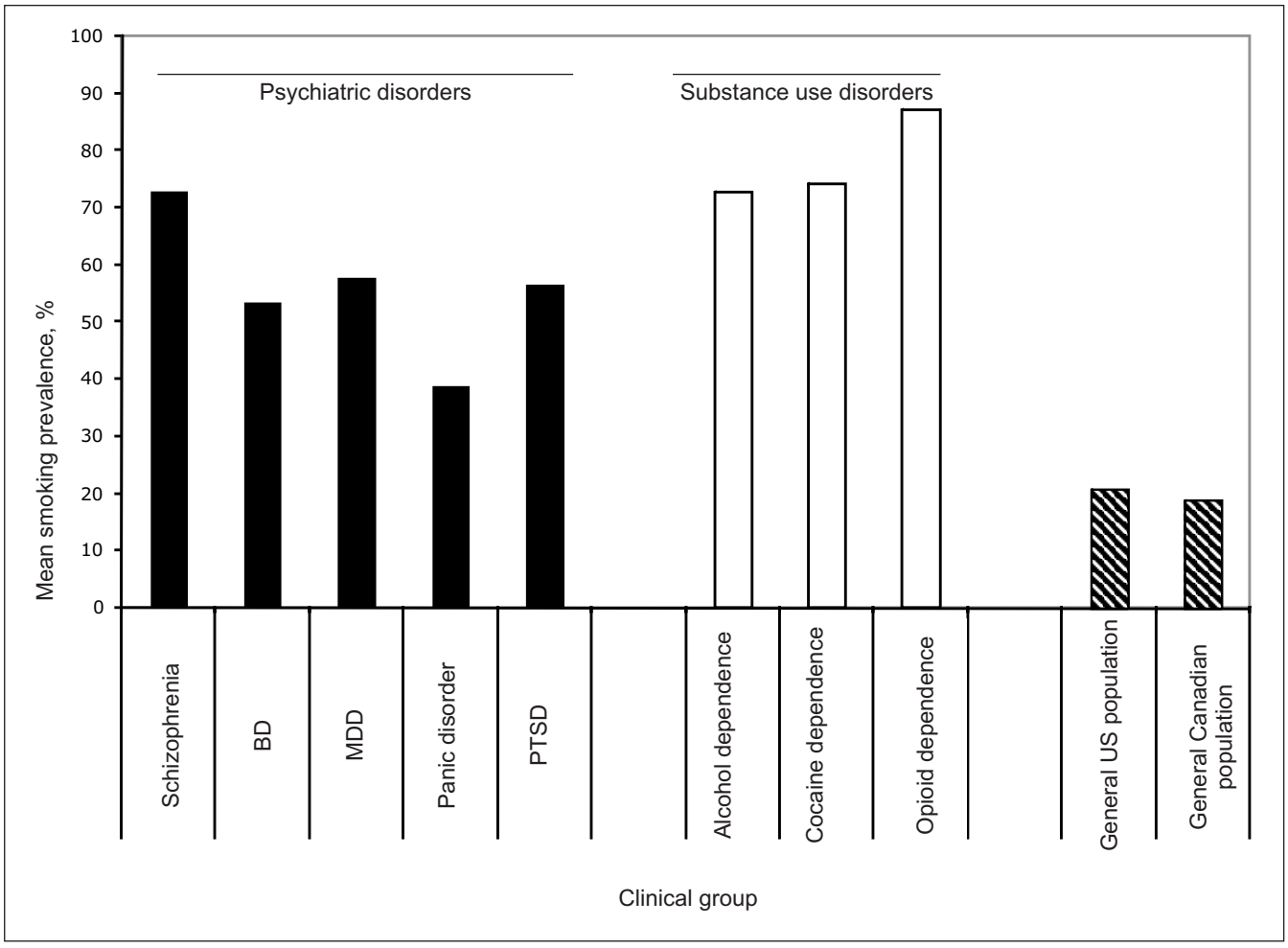
Nicotine modulates several neurotransmitter systems that are involved in the pathogenesis of MHA disorders, including DA.[10,15,16] The reinforcing effects of nicotine are mediated through activation of presynaptic nAChRs located on mesolimbic DA neurons.[17,18] The role of mesolimbic DA neurons in mediating the reinforcing effects of nicotine is suggested by rodent studies demonstrating that lesions of the VTA reduce nicotine self-administration, as well as local infusions of the nAChR antagonist MEC into the VTA.[19,20] It has also been observed that nicotine withdrawal leads to reductions in central DA in rodents[21] and urinary catecholamine excretion in human smokers.[22]

Nicotine promotes the release of other neurotransmitters including acetylcholine, endogenous opioid peptides, GABA, Glu, norepinephrine, and serotonin, which are also involved in the pathogenesis of MHA disorders.[18] These findings provide a heuristic link between cigarette smoking and the pathophysiology underlying MHA disorders.

Neuroimaging

Functional (for example, PET and fMRI) and structural (for example, computed tomography and MRI) brain imaging methods have become vital tools in the investigation of pathogenesis, diagnosis, and new treatment strategies of psychiatric disorders. However, there are only a handful of neuroimaging studies that have examined nicotine and tobacco effects in MHA smokers. DA release in ventral striatum has been measured in cigarette smokers using [11C]raclopride PET imaging. Smoking a denicotinized cigarette produced less DA release, compared with smoking a regular cigarette, confirming that nicotine is the agent responsible for an increase in central DA levels.[23,24] Further, smoking a nicotine-containing cigarette increases self-reported mood to a higher extent than smoking a cigarette lacking nicotine.[24] Cigarette smokers have a low density of D_2 receptors in striatum, measured by the PET ligand [18F]fallypride,[25] consistent with results from other addiction neuroimaging studies.[26] Another PET imaging study showed a positive correlation between the amount of inhaled nicotine and nAChR occupancy.[27]

Figure 1 Prevalence of cigarette smoking in clinic- and hospital-based populations with psychiatric and substance use disorders



Schizophrenia

An fMRI study in smokers with and without schizophrenia showed that nicotine reduced sensorimotor gating (prepulse inhibition) deficits, and that this was associated with activation of limbic regions and striatum both in patients and in control subjects.[28] Jacobsen et al[29] reported that nicotine improves activation and functional connectivity of brain regions (for example, hippocampus) that mediate working memory task performance using event-related fMRI methods. Further, a MRI structural brain imaging using voxel-basel morphometry demonstrated that reduced grey matter volumes in schizophrenia with comorbid tobacco addiction, compared with nonsmoking patients with schizophrenia and healthy control subjects.[30]

Affective Disorders

A PET study using [11C]clorgyline as a radiotracer[31] demonstrated that MAO-A is reduced in healthy cigarette smokers (that is, smokers without mental illness). During depression, brain MAO-A is known to be elevated. We suggest that people with affective disorders may use cigarette smoking to remedy elevated MAO-A levels, which appear to be a risk factor for MDD.[32]

Posttraumatic Stress Disorder

Using [11C]flumazenil PET, combat veterans suffering from PTSD had significant lower GABA-A binding, compared with veterans without PTSD.[33] Moreover, Czermak et al[34] studied the role of nAChR using [123I]5-IA PET imaging in PTSD patients and found a significantly higher nAChR binding in the mesiotemporal cortex, compared with control subjects.

Genetics

Several studies have evaluated genetic factors as determinants for comorbid tobacco use in MHA disorders. For example, the comorbidity between smoking and depression may be due to a common set of genetic factors that contribute both

to depression and to smoking. The available support for common genetic influences is limited, but growing. Kendler et al[35] examined 1566 pairs of female twins from the Virginia Twin Registry using a best-fitting bivariate twin model and found evidence for shared genetic factors to explain the association between ever smoking and lifetime MDD. These findings were extended in a recent study of male twins from the Vietnam Era Twin Registry showing that shared genetic factors predispose to MDD and daily smoking as well as MDD and TD.[36] In contrast, a case–control family study found evidence for shared familial vulnerability to dysthymia and heavy smoking, but not for MDD and heavy smoking.[37] Shared etiology between depression and smoking may vary by how depression and smoking are measured as well as the levels of depression and smoking.[38,39] Accordingly, shared genetic liability may better explain the comorbidity between MDD and habitual smoking, and the analytic approach may account for some of the differences across studies.[38]

Genetic variation in several postsynaptic DA D_2 receptors (1, 2, and 4) and the DA transporter (SLC6A3) have been investigated for MHA disorders (for example, schizophrenia and cocaine dependence) and have been implicated in adult cigarette smoking behaviour.[40,41] Polymorphisms in SLC6A3 have been associated with lower rates of smoking and longer periods of smoking abstinence.[42] Regarding smoking and depression, smoking for stimulation and for negative affect reduction have been shown to be higher among smokers who had greater depression symptoms and who were homozygous for the short alleles of the DA D_2 receptor 4, but not for those with at least one long allele of the DA D_2 receptor 4.[43] The DA D_2 receptor 2 has also been shown to play a role in adolescent smoking uptake. The likelihood of adolescent smoking progression increased significantly with each additional DA D_2 receptor 2 A1 allele, and this effect was accentuated among those with higher levels of depression.[44] These studies support interacting effects for dopaminergic genes and depression symptoms in adolescent and adult smoking practices.

DA D_2 receptors 1[45] and 2[40,41] polymorphisms have been associated with differences in smoking behaviour, and polymorphisms in the DA D_2 receptor 4 have been associated with smoking and depression.[43]

The primary hepatic enzyme system involved in the metabolism of nicotine to cotinine is CYP 2A6. Interestingly, there is evidence that polymorphisms in CYP 2D6 can determine smoking cessation responses to sustained-release bupropion,[46,47] and thus allelic variations in candidate genes related to smoking in MHA disorders may have pharmacogenetic treatment implications.

Psychological Mechanisms

Distress Tolerance and Negative Affect. Several investigations have focused on distress tolerance and negative affect as potential moderators for smoking cessation. Distress tolerance is defined as the behavioural tendency to pursue a goal despite encountering different forms of affective discomfort that may result from perceived psychological or physical distress. Brown et al[48] provided evidence that early smoking lapses and smoking outcomes in general are predicted not only by the intensity or severity of nicotine withdrawal but also by individual differences in the ability to tolerate and persist in smoking cessation despite emotional discomfort and distress. Brandon et al[49]demonstrated that pretreatment distress tolerance predicted sustained abstinence from smoking at 12-month follow-up; outcome prediction was independent of other significant predictors (for example, sex, TD, negative affect, and self-efficacy). Moreover, rapid increases in negative affect were associated with smoking relapse, as opposed to slow-changing shifts in stress and negative affect.[50] Accordingly, it has been proposed that treatment for early-lapse smokers should include interventions to address distress tolerance.[51]

Anxiety Sensitivity. AS reflects traitlike, individual differences in beliefs about the extent to which the experience of anxiety or fear will cause illness, embarrassment, or additional anxiety; it can be defined as the fear of anxiety-related sensations. People high in AS are more alert to anxiety-provoking stimuli and more motivated to avoid anxiety-provoking stimuli.[52] Zvolensky et al[53] have proposed a panic–smoking affect regulation model, which posits that AS is linked with heightened motivation to smoke to reduce the negative affect and uncomfortable bodily sensations associated with panic anxiety. In noncomorbid smokers, AS is correlated with smoking to reduce negative affect; similar results have been found in people with a history of MDD.[54] In another study, Zvolensky et al[55] demonstated that AS predicts the intensity of nicotine withdrawal symptoms during the first week of a quit attempt, and this was independent of panic history, negative affect, sex, cigarettes per day, TD, and age of smoking onset. Higher levels of AS have also been associated with early smoking relapse in people with past MDD.[54]

Personality Factors. Eysenck[56] suggested that addictive behaviours are developed within certain people because they serve various useful functions, the nature of which are related to the personality profiles of the people in question. Two types of traits are consistently associated with smoking: those that are approach-related (variously labelled, for example, extraversion, novelty seeking, and impulsivity) and those that are avoidance-related (for example, neuroticism and harm avoidance).[57] Terracciano and Costa[58] found that

among elderly people, current, compared with never, smokers had higher scores on neuroticism and lower scores on agreeableness and conscientiousness (with former smokers scoring in the middle). Smokers were further characterized by high impulsiveness and excitement-seeking, and low self-discipline and deliberation. Zuckerman and Kuhlman[59] found that impulsive sensation-seeking was the only personality factor that predicted smoking and drug use. Gilbert et al[60] found that trait depression and neuroticism predicted larger increased abstinence-associated negative affect in a group of female smokers asked to abstain for 31 days (compared with female smokers who continued to smoke). A meta-analysis of 25 cross-sectional studies of healthy adult smokers by Munafo et al[57] indicated that both elevated extraversion and neuroticism were linked to an increased likelihood of being a smoker, although effect sizes were small. A better understanding of individual differences in personality traits as potential predictors of smoking initiation and persistence may be integral to prevention and treatment efforts, given the compounding effects of comorbid personality disorders and traits in smokers with MHA disorders.

Psychosocial Determinants. There is evidence that cigarette smoking acts as a behavioural filler for patients with chronic mental illness, and promotes social interactions.[61] In fact, cigarette smoking in MHA smokers is reported as more desirable than food or shelter[62]; one report suggested that 27% of disability income is spent on cigarettes by smokers with schizophrenia.[63] Moreover, mental health staff may use cigarettes in a token economy to reward desirable behaviours (medication adherence) and negatively reinforce undesirable ones (for example, aggression and poor hygiene). MHA treatment settings are often a strong reinforcer of smoking behaviour, given the ubiquity of smoking and tolerance for these behaviours on treatment campuses.[64]

Review of Evidence for Tobacco Use in Specific MHA Disorders: Implications for Treatment Development

While higher rates of smoking in MHA disorders have been well-described, most published studies of MHA disorders have not addressed the role of nicotine and tobacco use as a confounding variable on study outcomes.[65] The failure to account for comorbid 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 owing to varying levels of withdrawal, or the misinterpretation of withdrawal symptoms from nicotine as being due to mental illness.

Schizophrenia

Patients with schizophrenia have higher rates of smoking (45% to 88%), compared with the general population, both in clinical[15,66] and in population-based[2] samples. In clinical samples, smoking rates are higher in inpatient (81.5%[67–70]), compared with outpatient (68.4%[11,71–78]), settings, 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 use of antipsychotic 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 (for example, an effort to alleviate side effects of medication by smoking).[77] 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 of patients with schizophrenia are nonsmokers, based on clinic-based smoking prevalence surveys[15]; and, smoking cessation in people with schizophrenia does not appear to lead to significant changes (either a worsening or improvement) in psychotic symptoms.[79–81]

Cross-sectional studies[71,78,82] have examined the associations between cigarette smoking and psychotic symptoms in schizophrenia. Goff et al[71] found that smokers with schizophrenia had higher total Brief Psychiatric Rating Scale scores than nonsmokers, and higher levels of positive and negative symptoms. Ziedonis et al[78] found increased positive symptoms, but reduced negative symptoms in smokers with schizophrenia, compared with nonsmokers. Heavy smokers had the highest positive and lowest negative symptom scores. While their sample was confounded by diagnostic heterogeneity, Hall et al[82] found that patients with chronic mental illness who were former smokers had less negative symptoms than patients with mental illness who were current smokers. However, recent controlled laboratory studies of tobacco abstinence,[83,84] along with data from controlled smoking treatment trials, have found no evidence for changes in psychotic symptoms with smoking cessation[79,80,85,87] or reduction[81] in schizophrenia. 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 (for example, trait factors) between smokers and nonsmokers may explain the results from cross-sectional studies.

Strong evidence for a pathophysiologically based vulnerability to smoking in schizophrenia relates to well-defined deficits in psychophysiological (for example, P50 gating) and neuropsychological function that appear to be improved or normalized by nicotine administration. For example, nicotine and smoking transiently normalize P50 gating and

smooth-pursuit eye movement deficits in schizophrenic patients and their first-degree relatives,[88–92] which appear to be mediated by deficient neurotransmission through alpha-7 nAChRs. In addition, nicotine and smoking have been shown to remediate working memory[29,84,95] and attentional deficits[84,96,97] in schizophrenia.

Cigarette smoking may reduce neuroleptic-induced parkinsonism,[98] and may worsen symptoms of tardive dyskinesia[99]; however, these effects have not been observed in all studies.[71,73,99] These observations are consistent with nicotine's enhancement of subcortical DA systems. Transdermal nicotine has been shown to reduce bradykinesia associated with haloperidol administration,[100] lending experimental support to the antiparkinsonian effects of nicotine.

Mood Disorders

Major Depressive Disorder. In clinical samples of people with MDD,[11,12,101,102] and in a population-based sample with clinically significant depressive symptoms,[103] smoking prevalence is 40% to 60%. Glassman et al[104] found that 61% of smokers presenting to a smoking cessation program in New York City had a past history of MDD. In a clinical sample of Hispanics in San Francisco (n = 547), Perez-Stable et al[105] reported that depressive symptoms, as determined by CES-D scale scores, of greater than 16 (suggesting clinically significant depression) were higher in current smokers (21.9% and 39.5% for males and females, respectively), compared with former (9.8% and 27.0%) and never smokers (11.8% and 18.5%). Similarly, in a population-based study of depressive symptoms and smoking, Anda et al[103] found that 39% of people with CES-D scale scores of greater than 16 were current smokers. It has also been observed that smokers with depressive symptoms have a much harder time quitting,[104,106] require more smoking cessation attempts to successfully quit,[107,108] and that smoking cessation is associated with the emergence of negative affective states.[101] Pharmacological studies have suggested that there are abnormalities in the brain DA reward system in smokers with MDD, compared with smokers without MDD, and that smoking appears to modulate negative mood states.[109] For patients with a history of MDD, smoking cessation may lead to a reemergence of MDD symptoms,[107,110] though this phenomenon has been questioned.[111,112] Further, Breslau et al[113] demonstrated that the severity of tobacco withdrawal appears to be worse in people with MDD or anxiety disorders, suggesting that severity of withdrawal may be a mechanism in the relation between these disorders and smoking persistence.

Cigarette smoking increases the risk for developing depressive symptoms.[114,115] Unidirectional studies have not assessed the effects of MDD on smoking behaviour, although studies suggest the relation is bidirectional with MDD.[116,117] However, it is not clear which comes first, depression or smoking, as study results are contradictory.[118,119] Moreover, there is evidence showing a positive correlation between TD and suicide risk.[120] Further studies of these relations are recommended using prospective designs.[3]

Bipolar Disorder. There have been several studies examining the comorbid smoking and BD,[11,121–125] and only one published treatment study to date.[126] Hughes et al[11] reported a smoking prevalence of 70% in BD patients from Minnesota, while Gonzalez-Pinto et al,[121] in patients with chronic mental illness in Spain, reported that 63% had lifetime histories of smoking, and that 51% were current smokers, compared with 33% in the control group. More recent studies[122,123] have found similarly high rates (55% to 70%) of smoking in BD. Corvin et al[123] found evidence that smoking may be more prevalent with the presence of psychotic symptoms in people with BD, but this finding was not supported in another study.[122] Smoking in BD is associated with poorer mania treatment response,[127] comorbid marijuana and alcohol use,[124,128] and acute rapid-cycling illness.[128] Moreover, in youth with BD, smoking is associated with more suicide attempts, substance use disorders, conduct disorder, and physical abuse.[125] Interestingly, Glassman et al[108] found that smokers with BD were at particular risk for depressive recurrence during smoking cessation.

Anxiety Disorders

Panic Disorder. Smoking prevalence in panic disorder varies widely across clinical studies, ranging from 19.2% to 56%.[2,129,132] Two longitudinal studies indicate that daily smoking is predictive of the onset of panic attacks, but not vice versa.[133,134] A third study prospectively examined the bidirectional relation between smoking, TD, and anxiety disorders in adolescents and young adults.[135] Prior regular smoking and dependence were associated with increased risk for new onset of panic attacks. However, owing to discrepancies between data analytic methods used, the authors could not conclusively rule out the potentially less common pathway of pre-existing panic attacks or disorder influencing the later development of TD. 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. The prevalence of smoking among patients with OCD appears to be the lowest among the anxiety disorders (7.7% to 22.4%).[129,132,136,137] Reasons for the lower occurrence of smoking in OCD are unclear, but could be related to the specific nature of OCD symptoms (for example, fears of disease and contamination) or a

combination of factors, including neurobiological and genetic factors, or social effects of having OCD.[136]

Posttraumatic Stress Disorder. Most empirical studies on PTSD and smoking have been conducted with combat veterans. Prevalence estimates of smoking range from 53% to 66% in combat veterans with PTSD.[138–140] Smoking prevalence has also been shown to differ based on high (56%), compared with low (39%), combat exposure.[141] Heavy smoking (more than 25 cigarettes per day) have been reported in PTSD, compared non-PTSD veterans (48% and 28%, respectively).[139] 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, compared with those without PTSD.[142]

In women with PTSD related to physical and sexual assault, Acierno et al[143] found a smoking prevalence of 44.4% (compared with 26.1% in those without PTSD). Recently, Vlahov et al[144] examined civilian smoking rates and prevalence after the United States terrorist attacks on September 11, 2001. Among people who were actively smoking prior to 9/11, 41.2% increased their smoking. People who increased their smoking were more likely to report symptoms of PTSD (24.2%), compared with smokers who did not increase their smoking (5.6%).

Regarding trauma exposure and risk of smoking, Anda et al,[145] controlling for confounding variables such as socioeconomic status and age, found that, compared with people who never experienced an ACE, those with a history of 5 or more adverse events (for example, verbal, physical, and sexual abuse, divorce, battered mother, substance abuse, mental illness, and incarcerated household member) had greater risks of early-onset smoking, ever smoking, and heavy smoking. Moreover, data from a 10-year prospective study indicated that trauma exposure predicted later development of TD, but that the risk of TD was significantly greater in people with PTSD.[146] When examining retrospective lifetime data, only PTSD, but not trauma exposure alone, predicted the subsequent development of TD. Collectively, these data suggest that PTSD, and perhaps trauma exposure, increases risk for the later development of TD. Sacco et al[147] have shown that cumulative ACEs in smokers with concurrent psychiatric disorders is higher than in nonsmokers with mental health disorders, and smokers and nonsmokers without psychiatric disorders.

Attention-Deficit Hyperactivity Disorder. ADHD is associated with higher rates and earlier onset of cigarette smoking,[148] 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.[149]

Addictive Disorders

The prevalence of tobacco use and dependence are among the highest in people with drug use disorders, including behavioural addictions such as pathological gambling.[150] The primary cause of death in addictive disorders as in mental disorders appears to be tobacco-related medical illness.[6,7]

Alcohol Use Disorders. The prevalence of smoking in people with alcohol use disorders is 70% to 80%.[151–153] 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.[154–155] Le et al[156] demonstrated that exposure to nicotine- enhanced alcohol consumption in rats. Blomqvist et al[155–157] have shown that the high-affinity nAChR antagonist MEC decreased alcohol consumption in high- but not low-alcohol preferring rats. More recently, Blomqvist et al[154] demonstrated that MEC, compared with a pretreatment placebo, decreased alcohol consumption and the rewarding effects of alcohol in humans.

Consumption of an alcohol, compared with a placebo beverage, acutely increases smoking behaviour,[158] and smoking status appears to be a clinical indicator for alcohol misuse.[159] For example, one study[160] found that smoking acutely increased the reinforcing value of alcohol; however, this effect was observed only following alcohol preexposure in men. In fact, similar to daily cigarette smoking, nondaily smoking also greatly increases (16-fold) the chances of hazardous drinking, compared with nonsmokers.[161] Moreover, in a population of smokers in alcohol treatment, urges to smoke increased during exposure to alcohol, compared with water cues,[162–164] and urges to smoke and drink were positively correlated during exposure to alcohol cues.[165] 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 behaviours, smoking urges (and smoking) become a conditioned response to alcohol cues, which serve as unconditioned stimuli.

Cocaine and Stimulants. People who use cocaine have high rates (about 80%) of comorbid cigarette smoking.[14,166] Significant reductions in cigarette consumption have been found after cocaine discontinuation.[167] The presence of cigarette smoking in people with cocaine dependence is associated with earlier onset of cocaine use, more severe use, more legal problems, and use by intravenous or smoked methods.[168]

Horger et al[169] 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[170] found that pretreatment with the centrally acting nAChR antagonist MEC, or deletion of the beta-2 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,[171] while a single pretreatment dose of MEC reduces cue-induced cocaine craving.[172] As nAChRs are present on mesolimbic DA neurons and nAChR stimulation augments DA release and metabolism,[17] blockade of nAChRs may modify DA responses induced by cocaine administration, thereby altering the reinforcing properties of cocaine.

Opioids. Greater than 80% of opioid-dependent patients smoke cigarettes.[14,173,174] The presence of depressive symptoms appears to increase the risk of smoking in methadone-maintained people.[174] Increases in methadone dose may lead to increased nicotine craving and cigarette consumption.[175] Conversely, heroin abstinence after detoxification has been associated with increased smoking consumption.[176]

Cannabis. The National Survey of Mental Health and Well-Being Study[177] 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 to 7.45) in current smokers. In people with BD, the early initiation of regular cannabis use is associated with cigarette smoking.[124] The lack of studies of tobacco and marijuana use comorbidity likely relates to the fact that cannabis is frequently used in combination with cigarettes and other addictions.

Gambling Disorders. Several studies have documented the higher prevalence of smoking in people with problem and pathological gambling. Compared with nondaily smokers seeking treatment for gambling problems, smokers were more likely to have been in substance abuse treatment, and had more severe gambling, psychiatric, and family and (or) social problems, gambled more frequently, and spent more money gambling, and reported higher craving and less control over their gambling urges.[178] Similar results with problem and pathological gamblers have been found, when comparing smoking and nonsmoking gambling groups, insofar as stronger urges to gamble were present in the smoker group,[179] and they reported more depression, suicidality, gambling-related arrests, alcohol and drug use problems, greater likelihood of being treated for a mental illness, and problems with nonstrategic (for example, slot machines) gambling activities.[150] These findings highlight the importance of developing effective interventions for smoking cessation in people with gambling disorders.

Conclusions and Recommendations

The systematic study of tobacco use comorbidity with MHA promises to further our understanding of the biology and treatment of each individual disorder. Moreover, identification of these high-risk smokers through careful screening of MHA in treatment settings will allow implementation of potentially effective interventions to reduce the rates of smoking and associated medical sequelae, given that tobacco-related medical illness is the leading cause of death in this subset of smokers.[5,6]

Thus there is a critical need for more research on biopsychosocial risk factors that explain the comorbidity of smoking in MHA, and more rationale and effective treatments directed toward smoking cessation in MHA, based on a better understanding of comorbid mechanisms. Specifically, studies of the temporal onset of tobacco use in MHA, abnormalities in nAChR and other receptor and neurotransmitter systems in MHA, and the genetics of the association between smoking, TD, and individual MHAs, are urgently needed. Progress in the treatment of TD in comorbid smokers[180] is dependent on our increasing understanding of this comorbidity, which will allow for the matching of the comorbid smoker to the optimal pharmacological and (or) behavioural therapy. Ultimately, advances in understanding of the etiology of comorbid MHA and smoking will reduce the social and economic burden of tobacco-related illness in Canadians with MHA.

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Résumé : Les mécanismes sous-jacents de la comorbidité du tabagisme dans les troubles de toxicomanie et de santé mentale

Nous discutons des explications possibles de la prévalence élevée de l'usage du tabac et de la dépendance au tabac (DT) chez les personnes souffrant de troubles de toxicomanie et de santé mentale (TSM). La base biopsychosociale de cette comorbidité est présentée et intègre des données probantes tirées d'études épidémiologiques et cliniques. Nous examinons également des données probantes qui suggèrent qu'une vulnérabilité partagée liée aux facteurs biologiques, génétiques et environnementaux pourrait être le mécanisme le plus parcimonieux qui explique l'association entre la DT et les troubles de TSM. Enfin, nous examinons les exemples de divers troubles de TSM qui sont associés à la DT, et suggérons des pistes de nouvelle recherche qui pourraient aider à l'élaboration de traitements rationnels et plus efficaces des comorbidités du tabagisme et des troubles de TSM.