

Nicotine addiction and comorbidity with alcohol abuse and mental illness

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The World Health Organization estimates that one-third of the global adult population smokes. Because tobacco use is on the rise in developing countries, death resulting from tobacco use continues to rise. Nicotine, the main addictive component of tobacco, initiates synaptic and cellular changes that underlie the motivational and behavioral alterations that culminate in addiction. Nicotine addiction progresses rapidly in adolescents and is most highly expressed in vulnerable people who have psychiatric illness or other substance abuse problems.

Tobacco use is the leading cause of preventable death in developed countries¹. Smoking commonly begins during adolescence, and about half of those who do not quit eventually die from smoking-related diseases². In the United States alone, smoking annually causes over 400,000 deaths and \$50 billion in medical costs³. The addictive power of tobacco is exemplified by the difficulty in quitting^{4–6}. Most smokers wish to quit and try repeatedly. About one-third of smokers attempt to quit each year, but fewer than 10% succeed. Despite imperative medical reasons, 50% of heart attack survivors and of those hospitalized for other serious smoking-related illness relapse to cigarettes within weeks of leaving the hospital.

Of the roughly 3,000 ingredients in cigarette smoke, nicotine is the main addictive component that motivates continued tobacco use despite its harmful effects^{4,6–10}. Nicotine is addictive in the absence of tobacco, and it supports self-administration, enhances reward from brain stimulation and reinforces preference for the place where nicotine is administered (place preference). It also produces a withdrawal syndrome that is relieved by nicotine replacement^{6–8,10,11}.

Tobacco use is most highly prevalent and is more intense in psychiatric patients and drug abusers^{12,13}. The comorbidity with mental illness is particularly high for schizophrenia and depression. These individuals may be more susceptible to nicotine addiction because tobacco provides desired positive mood influences¹⁴. Furthermore, they often experience more severe withdrawal symptoms, making it more difficult to quit. A great majority of those who abuse other substances also smoke, and there is a particularly strong correlation between smoking and abuse of the other most commonly abused drug, alcohol. More severely dependent drinkers smoke more and

are less likely to quit. Thus, particularly vulnerable groups within the overall population consume a disproportionately high fraction of all the cigarettes that are smoked¹².

Smoking begins in adolescence

The vast majority of those who initiate tobacco use are young. In the US, more than 60% of young people try smoking, and about one-third to half of them become daily smokers¹⁵. In those who initiate smoking, cigarette consumption escalates over a couple of years, but the addiction process proceeds quickly in adolescents^{5,16}. Nearly one-quarter of the adolescents report symptoms of addiction at about the time they establish a routine of smoking on a monthly basis. In young rats, synaptic changes and neuroadaptations to nicotine occur after only one exposure^{17,18}. In addition, adolescent rats show hypersensitivity to the reinforcing actions of nicotine, as demonstrated by intravenous self-administration and conditioned place preference^{19,20}.

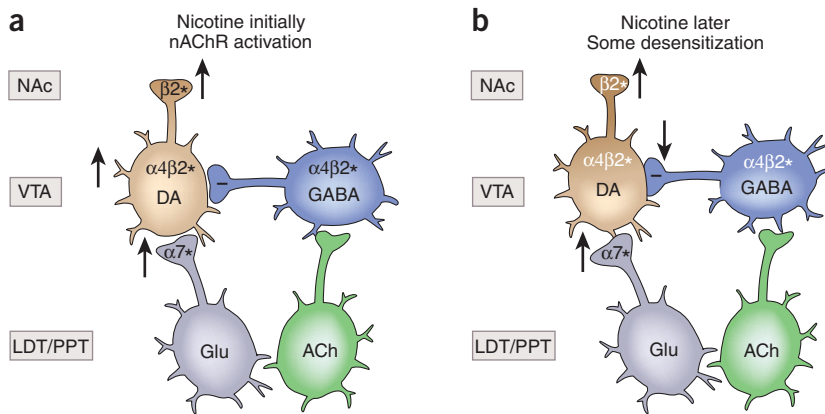
Tobacco can have positive effects on behavior and mood, but the first exposure to smoking often highlights the aversive impact^{21–23}. Adolescents, however, report fewer aversive effects and more positive effects than adults after their first smoking episode¹⁶. Furthermore, cigarettes are an ideal drug delivery system. Smokers adjust their dose precisely to avoid discomfort while achieving the most desirable impact^{5,6}. Once addicted, smokers report pleasure, arousal, relaxation, improved attention, reduced anxiety, relief from stress, relief from hunger and eventually relief from withdrawal symptoms⁵. Nicotine is a mood leveler in humans and other animals, causing arousal during fatigue and relaxation during anxiety.

Smoking is a learned (conditioned) behavior reinforced by nicotine. Cigarettes are excellent vehicles for the conditioning because the dosing via puffs is precise and repeated very often^{5,6}. Furthermore, the drug-taking behavior is associated with common events of the day, such as waking in the morning. The behavioral conditioning occurs more frequently, and is associated with more common everyday events, for cigarettes than for any other addictive drug. Therefore, the associations that become cues for smoking are almost unavoidable parts of smokers' lives.

In summary, adolescents experience aspects of dependence after only a few cigarettes, and nicotine exposure in adolescent rats increases self-administration tested later in life²⁴. The conditioned association of the

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Figure 1 A simplified illustration of several synaptic connections and nicotine-induced events that control DA release in the NAc. **(a)** Initially, nicotine causes some activation of most nAChR subtypes. The active presynaptic $\alpha 7^*$ nAChRs enhance glutamatergic excitatory drive (upward arrow), whereas active $\alpha 4\beta 2^*$ nAChRs directly excite DA neurons (upward arrow). This coincidence of presynaptic glutamate release and postsynaptic firing increases the likelihood of synaptic potentiation (for example, LTP). The cholinergic input from the LDT/PPT (laterodorsal tegmentum and pedunculopontine tegmentum) provides excitatory drive onto GABAergic interneurons. **(b)** The more prolonged presence of nicotine causes some desensitization (indicated by nAChRs in white text), particularly of subtypes containing the $\beta 2$ subunit. As a consequence, direct nicotine excitation of VTA DA neurons ceases, and GABA interneurons decrease their inhibition (downward arrow) onto VTA DA neurons. Although the nAChR subtypes are not perfectly segregated as shown, they are the main subtypes mediating nicotinic influence at the given locations, as shown in rodent studies.

addictive drug with common daily events motivates progression along the path to daily cigarette use and spurs relapse during abstinence.

Mesocorticolimbic dopamine system

Nicotine binds selectively to nicotinic acetylcholine receptors (nAChRs), which are ligand-gated cationic channels that normally bind acetylcholine^{25,26}. Neuronal nAChRs are pentameric, containing combinations of α and β subunits or exclusively α subunits, and in the mammalian brain only $\alpha 7$ subunits commonly form homo-oligomeric nAChRs. Because nAChRs are widely distributed, nicotine influences cellular events and produces neuroadaptations in many brain areas that are directly or indirectly important during the addiction process^{23,27}.

Although many areas of the brain participate, the mesocorticolimbic dopamine (DA) system has a vital role in the acquisition of behaviors that are inappropriately reinforced by psychostimulant drugs, including nicotine^{4,6–8,10,28}. An important dopaminergic pathway originates in the ventral tegmental area (VTA) of the midbrain and projects to the prefrontal cortex as well as limbic and striatal structures, including the nucleus accumbens (NAc). A wide range of evidence supports the role of the mesocorticolimbic DA system in nicotine addiction^{4,7,8}. For example, blocking DA release in the NAc with antagonists or lesions attenuates the rewarding effects of nicotine, as indicated by reduced self-administration^{11,28}. That result is consistent with the general finding that addictive drugs (such as cocaine, heroin and amphetamine) elevate DA in the NAc^{8,9}.

Recent, more sophisticated theories explain the mounting data that contradict the simplest notions about the rewarding properties of DA^{8,9,29,30}. Clearly, DA concentrations in the NAc are not a direct indication of reward. Rather, DA may participate in the ongoing associative learning of adaptive behaviors as an animal continually updates a construct of environmental saliency. The hypothesis suggests that addictive drugs act upon mechanisms that normally underlie learning

and memory^{9,17,29}. Thus, the functions of DA within the overall mesocorticolimbic system involve the learning and integration of salient environmental information. Subsequently, that information is used in the preparation, initiation and execution of behaviors that serve a beneficial goal^{8,9,29,30}.

Nicotine influences synapses of the VTA

Nicotine obtained from tobacco reaches the brain in 10–60 seconds, and is initially at a concentration of roughly 100–500 nM in the arterial blood, lung and brain^{5–7,10,31}. The distribution half-life of approximately 8 minutes dictates the initial actions of nicotine. The elimination half-life of about 2 hours allows nicotine to accumulate with ongoing smoking and persist for hours. Thus, smokers often deliver a small pulse of nicotine each time they smoke, and nicotine accumulates and lingers in the body (and brain) as the day progresses.

Upon smoking, nicotine initially activates nAChRs throughout the brain, including those on VTA DA neurons (**Fig. 1a**). Nicotine-induced activity of nAChRs produces a direct depolarization of the DA neurons, causing an increase in burst firing and overall firing rate^{10,29,32–34}. The nAChRs on the VTA DA neurons are mainly composed of $\alpha 4$ (ref.

35) and $\beta 2$ (refs. 36,37) subunits, in combination with other nAChR subunits³⁸. After a few minutes, the high-affinity $\alpha 4\beta 2$ -containing ($\alpha 4\beta 2^*$) receptors, in particular, desensitize (**Fig. 1b**), which decreases or terminates the direct stimulation of the DA neurons by nicotine^{32,39}. Microdialysis studies in rats show, however, that a single injection of nicotine elevates DA in the NAc for hours^{8,40}. Synaptic changes in the circuitry that controls the firing of VTA DA neurons produce the prolonged DA signal in the NAc.

The VTA receives massive convergent afferent inputs, including glutamatergic projections from the prefrontal cortex and GABAergic projections from the NAc and ventral pallidum^{10,41,42}. Another major source of innervation into the midbrain DA areas arises from the nearby pedunculopontine tegmentum (PPT) and the laterodorsal tegmentum (LDT), which are a loose collection of cholinergic neurons interspersed with GABAergic and glutamatergic neurons⁴². The PPT projects mainly to the substantia nigra compacta, and the LDT projects mainly to the VTA. The PPT and LDT contribute to events associated with drug taking²⁷, as shown by the observation that lesions in the PPT reduce nicotine self-administration⁴³. Although the VTA receives a strong excitatory glutamate input from the prefrontal cortex, that excitation is mainly onto DA neurons that project back to the cortex, not to the NAc⁴¹. Rather, the PPT and LDT provide the main glutamatergic excitation to the DA neurons projecting to the NAc (**Fig. 1**)⁴².

Glutamatergic afferents onto DA neurons commonly have presynaptic nAChRs composed of $\alpha 7$ subunits^{10,18,29,40}. Because $\alpha 7$ -containing ($\alpha 7^*$) nAChRs have a relatively low affinity for nicotine, the low concentrations of nicotine achieved by smokers do not strongly desensitize the $\alpha 7^*$ nAChRs (**Fig. 1**)^{32,39}. Thus, the activity of presynaptic $\alpha 7^*$ nAChRs enhances glutamatergic afferent excitation onto DA neurons while nicotine concentrations are elevated^{10,18}. The enhanced presynaptic glutamate release is paired initially with the increased firing of the postsynaptic DA neurons caused by $\alpha 4\beta 2^*$ nAChRs before they desensitize.

The combination of enhanced presynaptic drive and strong postsynaptic response favors the production of long-term synaptic potentiation (LTP) of the glutamatergic afferents (Fig. 1a)⁴⁴. Even though nicotine directly activates $\alpha 4\beta 2^*$ nAChRs on the DA neurons for only a short time before those nAChRs desensitize, that brief enhanced depolarization of the postsynaptic DA neurons is sufficient to produce LTP when paired with the boosted glutamate release caused by presynaptic $\alpha 7^*$ nAChRs.

While those nicotine-induced mechanisms enhance glutamatergic excitation of DA neurons, related mechanisms decrease the inhibition from GABAergic interneurons in the midbrain. Although a small subset of DA neurons receive cholinergic inputs from the PPT and LDT, there is greater cholinergic innervation and endogenous excitatory drive of GABAergic interneurons in the VTA (Fig. 1)⁴⁵. That endogenous cholinergic activity has a significant excitatory influence over the firing of inhibitory VTA GABAergic interneurons through the $\alpha 4\beta 2^*$ nAChRs^{10,40,46}. Although other minority subtypes are present, $\alpha 4\beta 2^*$ nAChRs make up the majority of the nAChR subtypes on midbrain GABAergic interneurons^{10,18,29,38–40,46}. As is the case for the DA neurons, nicotine desensitizes the $\alpha 4\beta 2^*$ nAChRs on the GABAergic interneurons in a matter of minutes (Fig. 1b). The inhibitory GABAergic activity declines rapidly because nAChR desensitization removes the direct excitation caused by nicotine and decreases the endogenous cholinergic drive onto the GABAergic interneurons arising from the PPT and LDT⁴⁰.

In summary, smokers deliver a small pulse of nicotine with each episode of smoking, and nicotine accumulates as the day progresses. That situation initially causes some activation of most nAChR subtypes, but then the prolonged low levels of nicotine favor significant desensitization of most non- $\alpha 7$ nAChR subtypes (such as $\alpha 4\beta 2^*$). As a result of these pharmacodynamics, nicotine initiates cellular and synaptic events in the VTA that enhance excitation and decrease inhibition to the DA neurons. As a consequence, DA neurons fire more frequently³⁴, and the concentration of DA is elevated in the NAc for a prolonged time^{8,40}.

Although most research has focused on the midbrain DA centers, nicotinic mechanisms are also important in the target areas of the DA projections. The striatum is richly innervated throughout by cholinergic interneurons, and this cholinergic activity regulates DA release^{47–50}, acting mainly through presynaptic non- $\alpha 7$ nAChR subtypes on DA terminals. When nicotine is applied *in vivo*, it desensitizes nAChRs on DA terminals (Fig 1b). By itself, this desensitization would decrease DA release—particularly release evoked by low-frequency action potentials (that is, tonic single-afferent pulses along the DA fibers)^{48–50}. However, by acting on the midbrain source of DA, nicotine causes DA neurons to fire more bursts of action potentials^{32–34}. Nicotine also acts at the fibers and terminals in the target neuron to alter DA signaling so as to favor DA release in response to phasic bursts while simultaneously depressing release in response to tonic, single action potentials. In that way, nicotine boosts DA concentrations in the NAc. Acting in the target region, nicotine alters the relationship between afferent activity along DA fibers and DA release, thereby altering DA signaling. Nicotine also acts in the target region to alter intrinsic GABAergic feedback mechanisms, thus modulating information processing along reward pathways^{51,52}. As research progresses, it is likely that such nicotinic mechanisms in the target areas will be better appreciated as important contributors to nicotine addiction.

Additional influences on reward, withdrawal and relapse

Although there is strong support for a role of DA and the overall mesocorticolimbic system in reinforcing nicotine use, evidence also indicates roles for other neurotransmitters and peptides. A fundamental role of

nAChRs in the brain is the presynaptic enhancement of neurotransmitter release^{25,26,29}. Enhanced release has been seen for GABA, glutamate and dopamine and also for other neurotransmitters that influence mood and emotional balance, such as serotonin, norepinephrine and endogenous opioids. Associated with opioid influences, chronic nicotine use upregulates μ -opioid receptors and alters the transcription factor CREB (cAMP response element binding protein)^{53,54}. Addictive drugs commonly alter CREB activity, which in turn influences the long-term behaviors associated with addiction⁵⁵ (also see the perspective by Nestler⁵⁶ in this issue). Likewise, those events are important for the reinforcing influences of nicotine^{53,54}. Environmental cues that are associated with the reinforcing properties of nicotine regulate CREB⁵⁴, and thus cues linked to smoking become conditioned stimuli that initiate molecular events contributing to the craving and relapse of abstinent smokers.

Environmental cues linked to withdrawal also may stimulate relapse. Withdrawal from nicotine decreases the sensitivity of reward systems, as detected by elevated thresholds for intracranial self-stimulation in rats^{57,58}. Nicotine elevates glutamate levels, and group II metabotropic glutamate (mGluII) receptors serve in a negative feedback capacity for homeostatic regulation of glutamate. It is hypothesized that among the neuroadaptations induced by chronic nicotine, altered mGluII receptor function decreases glutamate levels and contributes to the discomfort of withdrawal⁵⁷. Stimuli repeatedly paired with such withdrawal discomfort come to elevate reward thresholds on their own⁵⁸. Thus, the deficits in reward pathways normally caused by nicotine withdrawal eventually arise from conditioned stimuli that then cue smoking to relieve the symptoms. The $\beta 4$ nAChR subunit is likely to have a role in withdrawal because mice lacking $\beta 4$ show much milder symptoms when nicotine withdrawal is induced⁵⁹. Often the withdrawal symptoms and the 'priming' cues arising from internal states are more severe for smokers with psychiatric illness, making abstinence more difficult.

Comorbidity with mental illness

Nicotine dependence is much more prevalent among psychiatric patients than in the general population^{12,13}. Most notable are schizophrenic patients, who have smoking rates of 70% to 90% compared to about 25% for the general population. In a US study, patients with mood, anxiety or personality disorders show nicotine dependence twice as commonly as the general population¹². Remarkably, 7% of the overall population—those who have a psychiatric disorder and are nicotine dependent—consume 34% of all cigarettes. Adolescent smoking is particularly important because early tobacco use is associated with higher risk of later psychiatric problems and, conversely, early behavioral problems are linked to a greater risk of later tobacco use. For example, the prevalence of psychiatric disorders is about 70% in adolescents who are daily smokers⁶⁰. Although attention-deficit/hyperactivity disorder (ADHD) does not increase smoking prevalence in all studies, children with ADHD often initiate smoking earlier and have more trouble quitting^{13,61}. In addition, depression and anxiety are associated with higher risk for smoking initiation and for transition to daily smoking⁶². An evaluation of female twins suggested that the relationship between lifetime smoking and major depression arises largely from familial factors (likely genetic) that predispose individuals to both smoking and depression⁶³.

It is commonly argued that psychiatric patients use tobacco for self-medication. That hypothesis applies most readily to schizophrenia. Nicotine normalizes several deficits in sensory processing associated with schizophrenia, and nAChRs influence those sensory events^{13,64}. Although nicotine seems to improve attention in schizophrenia, it does not improve most symptoms⁶⁵. However, there is other intrigu-

ing evidence linking nAChRs and schizophrenia. The chromosomal region containing the nAChR $\alpha 7$ subunit is linked to genetic risk for schizophrenia, and $\alpha 7$ expression is reduced in schizophrenics^{13,64}. The self-medication hypothesis also may have some validity among ADHD patients. Nicotine increases the release of DA and improves attention, and similar effects are produced by stimulant drugs used to treat ADHD. Cigarettes also may provide a medicating influence because an unknown ingredient inhibits brain monoamine oxidase, and monoamine oxidase inhibitors have antidepressant actions^{66,67}.

Another factor that may exacerbate nicotine addiction arises from psychiatric medications. For example, antipsychotic drugs block DA receptors, and nicotine can overcome this action by enhancing DA release and reducing unwanted side effects. Indeed, schizophrenics who smoke have a lower incidence of neuroleptic-induced parkinsonism, and haloperidol increases smoking in schizophrenics²¹. This influence is only part of the motivation for smoking, however, because even first-episode patients who have not received antipsychotic drugs have a high incidence of smoking⁶⁸.

The links between stress, depression, anxiety and tobacco use also are contributing factors for comorbidity. Depression sensitizes smokers to the influences of stress, which increases the motivation and vulnerability for drug use⁶⁷. During the acquisition phase, stress increases the sensitivity to addictive drugs, making the individual more susceptible to drug reward. During abstinence, stress can stimulate reinstatement of drug seeking and drug self-administration. Craving and relapse can be elicited by the drug itself or by environmental cues that become salient through their repeated association with previous use. Just as environmental events associated with nicotine withdrawal serve as priming cues for drug seeking⁵⁸, the stress response mimics a motivating internal state⁶⁹. Depression and anxiety often accompany nicotine withdrawal, particularly for abstinent smokers with psychiatric illness, and relief from specific aspects of those symptoms motivates relapse. Thus, smokers become conditioned to expect nicotine to provide partial relief from stress and depression as it does from the symptoms of withdrawal⁶⁷. This hypothesis has mechanistic support because stress produces synaptic plasticity in the VTA similar to that produced by nicotine^{17,70}. Furthermore, anhedonia often accompanies mental illnesses such as schizophrenia and depression. By boosting DA release, nicotine may ameliorate particularly the anhedonic aspects of the illness. It is reasonable to conclude that common underlying mechanisms influencing motivation and behavior contribute to the high comorbidity between forms of mental illness and nicotine addiction.

Comorbidity with alcohol

Nicotine and alcohol seem to share few pharmacological similarities. Nicotine has specific receptors, promotes alertness and is proconvulsant, whereas alcohol affects multiple receptor types, diminishes alertness and is anticonvulsant. Although both drugs produce tolerance and dependence, the characteristics of the withdrawal syndromes also differ markedly⁷¹. Despite these clear distinctions, there are remarkable commonalities between the two drugs, including their legal status and wide use.

The prevalence of nicotine dependence is very high among alcohol abusers¹². In addition, the amount of tobacco smoked is positively correlated with the amount of alcohol consumed and the severity of alcohol dependence. Although a past history of alcohol dependence does not influence the subjective effects of nicotine, it does render nicotine more reinforcing than for those who have never been alcohol dependent⁷². There also may be shared genetic influences over the development of nicotine and alcohol dependence (also see Crabbe and Lovinger⁷³, in this issue). Twin studies indicate a substantial genetic

correlation between nicotine and alcohol dependence, with only a modest environmental contribution⁷⁴. A potential mechanistic link arises from the observation that smokers report less intoxication from the same amounts of alcohol than either nonsmokers or former smokers and that result is not due to differences in alcohol metabolism⁷⁵. Low responsiveness to alcohol is a risk factor for the development of alcohol dependence⁷⁶, and chronic nicotine use may decrease the effects of alcohol, thereby increasing alcohol consumption and dependence. Nicotine and alcohol also both relieve pain, and that action requires the GIRK2 potassium channel⁷⁷. Although nicotine does not act directly on GIRK channels, the overall action demonstrates a convergence of drug actions on a common effector protein. Further convergent action is indicated by animal studies of motor activity and body temperature that show cross-tolerance for nicotine and alcohol⁷⁸.

Emerging results from human brain imaging suggest that neuroadaptations and neurotoxicity produced by chronic alcohol abuse may also be altered by smoking. When alcoholics stop drinking, they show a time-dependent increase in the number of neuronal GABA_A receptors. There also is evidence that increased GABA_A receptors result in more severe withdrawal symptoms. Smoking reduces upregulation of GABA_A receptors and may reduce the severity of alcohol withdrawal⁷⁹. It is possible that nicotine boosts DA signaling that is diminished during alcohol withdrawal. If alcohol enhances GABA inhibition of the mesolimbic DA neurons, chronic nicotine may counter the upregulation of GABA_A receptors as well as acting acutely to decrease GABAergic inhibition by desensitizing nAChR subtypes that help drive GABA interneurons (Fig. 1b).

The link between nicotine and alcohol use is of particular importance for adolescents. Initiation of smoking at an early age is a risk factor for the development of alcohol dependence and other substance-abuse disorders⁸⁰. A large Finnish study gathered data on 14-year-olds and followed them until age 32. Regular smoking at age 14 was the most powerful predictor of drunk driving offenses at age 32 (ref. 81). A key issue is whether exposure to nicotine during development increases alcohol use and dependence. There could be psychosocial influences as well as a pharmacological role for smoking in later substance abuse. Animal studies show that chronic nicotine administration does increase alcohol self-administration, supporting a possible causal link between smoking and alcohol reinforcement⁸². Although unproven, it is possible that preventing or delaying initiation of nicotine use in adolescence would reduce development of alcohol abuse later in life.

Commonalities between nicotine and alcohol also occur at the molecular and genetic level. Genetically selected lines of mice and rats show different specific behavioral responses to ethanol, and some of those animals also have differing reactions to nicotine. Rat and mouse lines sensitive to the hypnotic actions of alcohol show a different sensitivity to the locomotor effects of nicotine^{83,84}, suggesting common genetic determinants for those actions. One genetic factor influencing nicotine and alcohol modulation of acoustic startle in mice is a polymorphism in the $\alpha 4$ nAChR subunit⁸⁵. The presence of alanine or threonine at position 529 of the $\alpha 4$ subunit influences the effects of nicotine and alcohol on the response to acoustic startle and to the severity of an alcohol withdrawal sign in mice⁸⁶. Studies with mice lacking the $\beta 2$ subunit have shown that those actions of nicotine and alcohol are mediated by $\alpha 4\beta 2^*$ nAChRs⁸⁵. These studies provide hints of possible molecular interactions between nicotine and alcohol. Indeed, ethanol alters the function of neuronal nAChRs, possibly by binding to a site analogous (but not identical) to the alcohol site proposed for GABA_A and glycine receptors⁸⁷. Even though the A529T polymorphism is in the intracellular loop of the $\alpha 4$ subunit and distant from the proposed alcohol binding site, it is possible that the polymorphism influences

the alcohol sensitivity of the $\alpha 4^*$ nAChR⁸⁸. Although the mechanistic details are not yet conclusively known, there are interactions between nicotine and alcohol at the $\alpha 4\beta 2^*$ nAChR. Other subtypes also are influenced, and additional complexities are likely to contribute to the commonalities between the two addictive drugs^{85,89}.

The substantial interactions between nicotine and alcohol raise the possibility of pharmacotherapies that could either simultaneously treat nicotine and alcohol dependence or treat alcohol dependence by blocking nAChRs that may contribute to alcohol consumption. The nonselective nAChR antagonist mecamylamine reduces the reinforcing actions of alcohol in humans⁹⁰, but this treatment is not practical because mecamylamine produces autonomic side effects. Several drugs that do not directly affect nAChRs show some promise: cannabinoid CB1 receptor antagonists and the anticonvulsant drug topiramate may be useful in treating both nicotine and alcohol dependence^{91,92}.

The common comorbidity of tobacco use with mental illness or drug dependence suggests that a more complete understanding of nicotine addiction will have a broad impact on society. The mechanisms underlying nicotine addiction may indicate common modes of treatment and prevention for particularly vulnerable members of the population.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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