

NCI Monograph 24

Tobacco and Alcohol: Understanding Co-Use to Reduce Cancer Incidence and Mortality

Chapter 6

Shared Physiological and Genetic Factors Contributing to Tobacco and Alcohol Co-Use

Chapter Contents

Introduction.....	355
Nicotine, Ethanol, and Biological Pathways in the Brain.....	358
General Overview of Neurophysiology	358
Dysregulation of Dopaminergic Signaling With Nicotine and Ethanol Use	360
Neuroimaging Studies.....	361
Shared Genetic Factors That Contribute to Tobacco and Alcohol Behaviors	365
How Genetic Studies Are Conducted	366
Challenges in Conducting Phenotype Assessments.....	368
Main Results From Genetic Studies	370
Drug Metabolism and Neuronal Response Genes	370
Genome-Wide Association Studies	371
The Potential for Personalized Medicine for Prevention and Cessation.....	379
Personalized Treatment for Tobacco Use	379
Personalized Treatment for Alcohol Use Disorders	380
Personalized Treatment for Comorbid Tobacco and Alcohol Use Disorders.....	381
Using Large-Scale Genetic Studies to Predict Cessation	382
Chapter Summary	383
Research Needs	386
Conclusions.....	388
References	394

Figures and Tables

Figure 6.1	Developmental Trajectory of Tobacco and Alcohol Use Disorders Is a Process With Multiple Stages	356
Figure 6.2	Key Brain Regions Affected by Nicotine and Ethanol Use	359
Figure 6.3	Large-Scale Brain Networks Implicated in Addiction Through Neuroimaging ...	363
Figure 6.4	Multiancestry Meta-Analysis Manhattan Plots for Smoking Behaviors and Alcohol Consumption.....	376
Table 6.1	Key Genome-Wide Association Studies of Tobacco and Alcohol	373

Appendices

Appendix 6A	Selected Genome-Wide Association Studies of Tobacco and Alcohol Published Since 2018.....	389
Appendix 6B	Literature Search Strategy.....	393

Chapter 6

Shared Physiological and Genetic Factors Contributing to Tobacco and Alcohol Co-Use

Introduction

Significant progress has been made toward identifying biological factors contributing to tobacco and alcohol use through large-scale human genetic studies of dependence and substance use disorders.^{1,2} Substance use disorders are complex diseases in which thousands of genetic variants contribute to an individual's overall risk. Indeed, thousands of genetic loci have been identified as contributing to tobacco and alcohol use. Studies have found that some of these genetic variants are associated either with tobacco or alcohol use, and some are associated with the use of both substances.¹⁻⁷

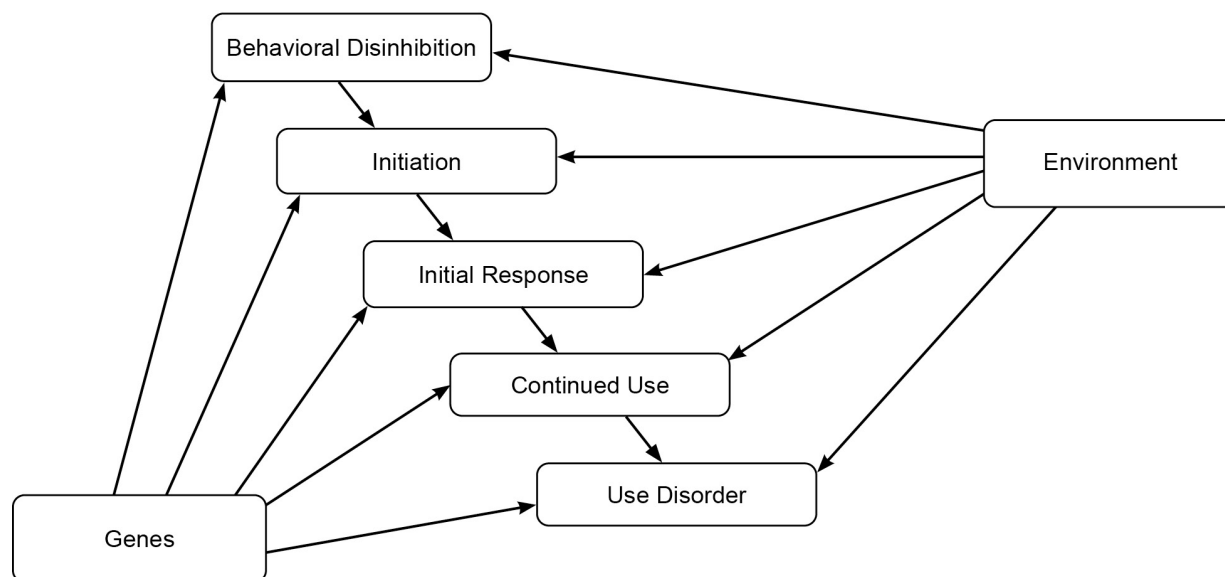
Throughout the 1990s and early 2000s, the prevailing methodology in genetic studies utilized family-based approaches when conducting whole genome studies or focused on candidate genes based on known physiological or biochemical pathways.⁸⁻¹⁰ A summary of those approaches applied to smoking behaviors was reviewed in the 2010 Surgeon General's report, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, and National Cancer Institute (NCI) Monograph 20, *Phenotypes and Endophenotypes: Foundations for Genetic Studies of Nicotine Use and Dependence*.^{8,10} The development of low-cost technologies for examining hundreds of thousands of variants across the genome has expanded researchers' ability to conduct large-scale agnostic association studies.¹¹⁻¹⁴ Agnostic association studies consider all regions of the genome without prior assumptions about the relevant area of the genome or type of genetic element of interest.¹⁵ These genome-wide association studies (GWAS) leverage very large sample sizes to achieve the statistical power needed to detect small-effect genetic variants and have been applied to both tobacco and alcohol.^{1,2,16}

This chapter discusses the physiological, cellular, molecular, and genetic factors contributing to tobacco and alcohol use. Overall, genetic studies have demonstrated that tobacco and alcohol use disorders, as well as other substance use disorders and psychiatric disorders, have both shared and unique genetic risk factors. The chapter describes overlapping genetics and corresponding neurophysiology contributing to the co-use of tobacco and alcohol, summarizing the biological pathways affected by nicotine and ethanol and describing findings from neuroimaging studies and genetics studies, particularly results from large GWAS. When discussing biological mechanisms, this chapter focuses on nicotine and ethanol. Nicotine and ethanol are the main drivers of the addictive processes for tobacco and alcohol, respectively. However, one important contrast between tobacco and alcohol is that ethanol is almost entirely responsible for alcohol-related carcinogenesis, while tobacco smoke is a complex mixture of thousands of compounds, including many which are toxic and carcinogenic.¹⁷⁻¹⁹ There is insufficient evidence to conclude that nicotine plays a direct role in carcinogenesis, although it does interact with some relevant pathways.²⁰

The initiation of tobacco and alcohol use and the progression from initiation and use to tobacco or alcohol use disorders is a process with multiple stages, as shown in Figure 6.1. Both environmental and genetic factors contribute to the development of dependence and disease, and different genetic factors contribute to tobacco and alcohol use patterns across different phases of use and development of use disorders.^{19,21} Further, biological and behavioral studies of tobacco and alcohol use address a wide range of phenotypes at different stages of the developmental trajectory of use. The combined influence of these factors on tobacco use and dependence are also highlighted in NCI Monograph 20.⁸ Notably, individuals may quit using tobacco or alcohol or make unsuccessful attempts at cessation at any point and thus move forward or backward along this trajectory. Therefore, this diagram is a simplification in that it is unidirectional and does not include additional feedback loops.

NCI Monograph 20⁸ emphasizes the importance of identifying endophenotypes (i.e., phenotypes related to the underlying mechanisms of disease), including those that are related to the adoption or maintenance of nicotine dependence. Further research identifying the phenotypes and endophenotypes underlying use and co-use of both tobacco and alcohol could refine the conceptual model presented in Figure 6.1 to incorporate factors in addition to behavioral disinhibition that influence initiation and continued use of tobacco and alcohol, including various patterns of use. Efforts are being made to characterize endophenotypes related to alcohol use,²² and some research has directly addressed endophenotypes of co-use and polysubstance use.²³ Large longitudinal neuroimaging studies such as the Adolescent Brain Cognitive Development (ABCD) and Healthy Brain and Child Development (HBCD) studies^{24,25} could facilitate identification of new phenotypes and endophenotypes related to co-use.

Figure 6.1 Developmental Trajectory of Tobacco and Alcohol Use Disorders Is a Process With Multiple Stages



Source: Adapted from Bierut 2011.²⁶

Tobacco use and alcohol use disorder may develop concurrently with first or early use, or use disorders may manifest more gradually or not at all.¹⁹ Alcohol use often occurs without characteristic features of dependence or use disorder; however, even alcohol use within the 2020–2025 U.S. Dietary Guidelines (≤ 2 drinks/day for men and ≤ 1 drink/day for women)²⁷ is associated with increased cancer risk.²⁸ Attention to alcohol use at all levels of consumption is important from the perspective of cancer prevention.²⁷ For example, a low level of alcohol consumption (1 drink per day) is associated with an increased risk for breast cancer among women (see chapter 4). Moreover, as discussed in chapter 4, there is a dose-response relationship between alcohol consumption and many cancers, and increased synergistic risk of head and neck cancer and squamous cell esophageal cancer associated with tobacco and alcohol use. Alcohol use disorders often involve higher levels of consumption and thus greater cancer risk.

As discussed in chapter 2, more than half of those who report current (past-year or past-month) tobacco use also report using alcohol. It should also be noted that, among U.S. adults in 2022, daily or near-daily cannabis use in the past month (5.3%) was approximately as prevalent as daily or near-daily alcohol use in the past month (4.4%).²⁹ Although discussion of co-use of cannabis with alcohol and/or tobacco is beyond the scope of this monograph, research to understand the interplay among tobacco, alcohol, and cannabis is increasingly important, given trends in cannabis use.

Most of the research as of 2026 has been conducted in adults, but a handful of longitudinal studies investigating precursors and the onset of alcohol use in childhood and adolescence are underway. The largest ($N = \sim 11,500$) and most comprehensive of these is the ongoing ABCD study,^{25,30} which investigates neurodevelopment among youth ages 10–20 years.^{31,32} Another key study is the HBCD study, a cohort designed to examine *in utero* effects as well as subsequent environmental exposures in infancy and beyond on ontogeny of brain development and ultimately substance use.²⁴

In most past studies, sex has not been directly examined to identify whether distinct genetic variants play differential roles in men and women. Where appropriate, this chapter incorporates discussion about whether sex differences have been examined or identified. Similarly, the field of human genetics has only recently begun a strong effort to recruit a diverse sample of participants at a large scale. For example, the *All of Us* Research Program, with recruitment launched by the National Institutes of Health (NIH) in 2018, is making such an effort.³³ Where available, data for previously underrepresented populations are presented in this chapter, describing similarities and differences between results from the initial European ancestry-based studies. Finally, one of the major challenges in the field is moving from the identification of genetic variants to understanding their biological function; this is especially difficult because most of the variants do not fall in genes with known or predicted impacts on molecular function. Research has expanded to begin to incorporate data from other “omics” resources, such as studying gene expression in the brain, epigenetic features, proteomics, and metabolomics.

Nicotine, Ethanol, and Biological Pathways in the Brain

Tobacco and alcohol are frequently used together, and high comorbidity exists between nicotine dependence and alcohol use disorder (see chapter 2).³⁴⁻³⁶ Furthermore, both substances target many of the same neuronal pathways in the brain, sometimes in a manner that accentuates the effect of the other substance and in other cases reduces it.

General Overview of Neurophysiology

As research reveals more about the brain, characteristics of its functions and complexity become even more challenging to describe and understand. For example, the brain used to be described primarily in terms of different functions of certain morphologically defined regions, such as the striatum, hippocampus, or prefrontal cortex. With advances in the technologies and computational analysis approaches used, it has become clear that each brain region is part of a network, comprised of complex connections of subregions, and that even within very small subregions, different cell types (e.g., neurons, interneurons, astrocyte, microglia) are found that confer unique neurophysiological signals.^{37,38} Such signals may be different between immediately adjacent cells.³⁹ Likewise, many psychoactive substances affect dopamine release and binding in key brain regions, and there has been a significant focus on understanding how substances disrupt the dopaminergic pathway and thereby lead to dependence.⁴⁰ In addition to dopamine, substance use also influences the release of norepinephrine, serotonin, glutamate, and acetylcholine. Furthermore, differences between individuals due to both genetic variation and environment, including past experiences or precursors, can confer different baseline levels of neurotransmitters and/or differential responses to substances according to functional changes of brain receptors.

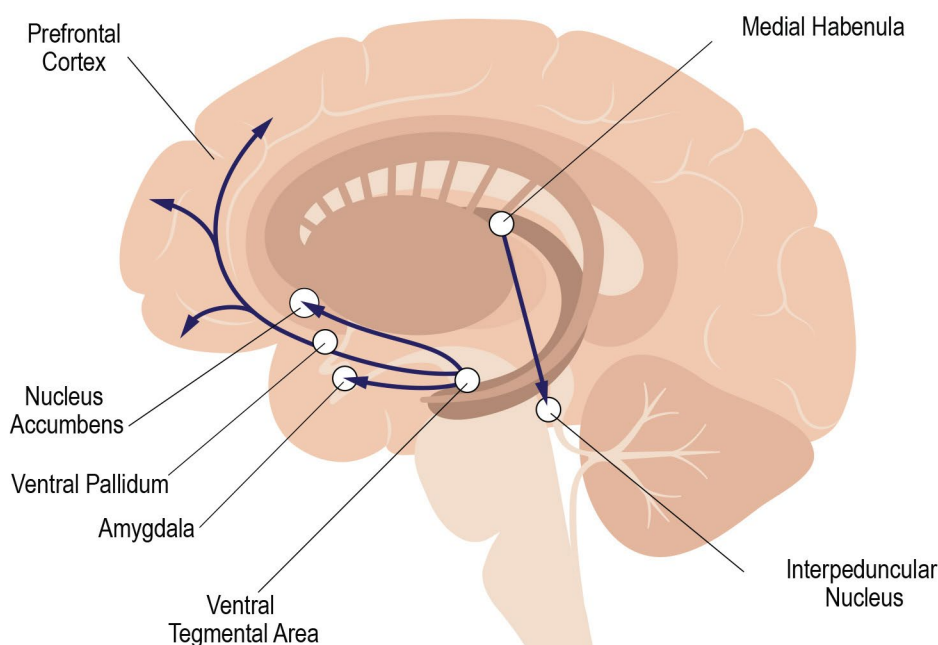
The neurophysiological mechanisms underlying substance use disorders have been described and studied in the context of three functional domains or mechanisms: (1) incentive salience, (2) negative emotional states, and (3) executive function; each of these is mediated by a distinct neurobiological circuit: (1) basal ganglia, (2) extended amygdala, and (3) prefrontal cortex, respectively.⁴¹ This triadic neurobehavioral model was primarily developed to explain the maintenance of use and return to use after abstinence in adults who have already progressed to substance use disorder. In addition, evidence also supports its relevance in explaining the onset and escalation of substance use earlier in life,⁴² demonstrating its importance across different stages of substance use and addiction. Furthermore, the triadic neurobehavioral model appears to apply to most or all substance use disorders.⁴³

Addictive substances—including nicotine and ethanol—affect these three major neurobiological circuits implicated in dependence and addiction. The neurobiological circuit implicated in incentive salience includes the nucleus accumbens, dorsal striatum, globus pallidus, thalamus, and ventral tegmental area (Figure 6.2).⁴¹ This system is a major pathway for dopamine, involving modulation of reward, motivation, and desire, and contains the cell bodies of neurons that, when stimulated, cause dopaminergic release in multiple other structures, including the nucleus accumbens.¹⁹ Nicotine, ethanol, and other addictive substances increase dopamine concentrations in the nucleus accumbens, leading to an urge or motivational drive to continue consuming these substances. In contrast, the extended amygdala recruits the brain's stress

systems, which drive feelings of negative affect during withdrawal states.⁴¹ The prefrontal cortex, which is involved in higher-order executive functioning, is dysregulated among individuals with substance use disorders and contributes to disadvantageous decision-making, impaired self-awareness, and dysregulated self-control and self-regulation.^{19,41,44,45} Intense feelings of craving and anticipation are further associated with the prefrontal cortex and intervals between use.⁴⁴

Importantly, addictive substances affect some of the same neurobiological circuits in overlapping but not identical ways, and are often used together or in a short time window. The effects of co-use may be additive, disinhibitory, or have other types of interactions. For example, additive effects of co-use of nicotine and ethanol have been demonstrated in rats.⁴⁶ The long-term effects on brain function from concurrent co-use of two or more addictive substances can be stronger than the effects of using either substance separately.⁴⁷ Accordingly, polysubstance use or co-use of multiple addictive substances has been considered a severity indicator in substance use disorders and is linked to poorer health outcomes and higher rates of return to use after treatment.⁴⁷⁻⁵⁰ Finally, in addition to shared effects of addictive substances on the brain, there are also substance-specific effects. For example, a pathway between the medial habenula and interpeduncular nucleus (IPN) contains numerous neuronal nicotinic receptors. These receptors have been widely studied for their role in the effects of nicotine and ethanol on behavior and the development of tobacco and alcohol use disorders,^{10,51,52} and were highlighted in the 2010 Surgeon General's report.¹⁰ Figure 6.2 illustrates the key brain regions affected by nicotine and ethanol use.

Figure 6.2 Key Brain Regions Affected by Nicotine and Ethanol Use



Source: Adapted from Koob & Volkow 2016.⁴¹

Dysregulation of Dopaminergic Signaling With Nicotine and Ethanol Use

All addiction processes affect the function of the brain. This includes substance use disorders and other mental health conditions that involve compulsive behaviors, such as gambling disorders, compulsive sexual behavior, eating disorders, and internet gaming addictions.⁵³ At its core, any kind of dependence or addiction involves cyclical changes in the production, release, and binding of dopamine in the brain.⁴¹ Increases in addictive behaviors occur as people seek out the specific substance or experience that leads to a transient increase in dopamine release, and an increasing amount of the experience or substance may be needed to elicit this response, a process referred to as “tolerance.”¹⁹ The fact that cross-tolerance (when repeated administration of one substance induces a decreased response to another substance) is associated with nicotine and ethanol co-use as well as use of other substances together with tobacco and/or alcohol^{54,55} has important implications for interventions addressing initiation and cessation in the context of co-use (see chapters 5 and 7). Furthermore, chronic use of addictive substances shifts baseline dopamine levels downward in animal models and some human studies, such that addiction is sometimes described as a hypodopaminergic state.⁵⁶ This results in increased craving and use of drugs of choice and reduced salience of other nondrug stimuli. Morel and colleagues (2019)⁵⁷ provide a comprehensive overview of the important role of dopaminergic neurons in modulating nicotine and ethanol reinforcement.

Most physiological studies of addictive behaviors have been conducted using rodent models.⁵⁸ Rodents and humans share similar brain structures, neuronal pathways, and genetic homology across the genome.^{41,59} However, it is important to recognize the limitations of animal models, as certain aspects of these models may not translate to humans. For example, most rodent studies employ a single inbred strain of mouse or rat for research,⁶⁰ and these genetically identical animals are assessed for behavioral measures believed to capture different aspects of the developmental trajectory depicted in Figure 6.1. In some studies, animals self-administer the substance, but methods for administration can vary according to access (limited, unlimited, choice between substance and water) and route of administration (oral or injection). When examining measures for tolerance or withdrawal, nicotine or ethanol are often injected by the investigator to ensure a consistent dose. Reviews of rodent behavioral paradigms provide additional detail.⁶¹⁻⁶³ Mouse and rat models have different strengths and weaknesses that have evolved over time. As genetic tools developed in the mouse have become standard in the rat, many investigators have transitioned to using the rat for studies of the neuroscience of psychiatric disorders because the processes fundamental to addictive behavior in humans are more similar to those in the rat than in the mouse.⁶⁴

Many human studies indicate that adolescent exposure to alcohol and/or tobacco leads to an increased risk of developing tobacco and alcohol use disorder in adulthood, as well as other substance use disorders.⁶⁵⁻⁶⁷ However, because co-use of tobacco and alcohol products in adolescence is common, it is difficult to disentangle in longitudinal human studies which substance accounts for what proportion of the subsequent development of a substance use disorder.⁶⁵ Chronic consumption of alcohol in rats may increase the rate of biotransformation of nicotine and its metabolites, and this may differ by sex.⁶⁸ Nicotine and ethanol also appear to have interactive influences on neuronal activity in rodents.^{46,69} These interactions may underly the observation that nicotine and ethanol have not only antagonistic but also synergistic effects in the brain.⁵²

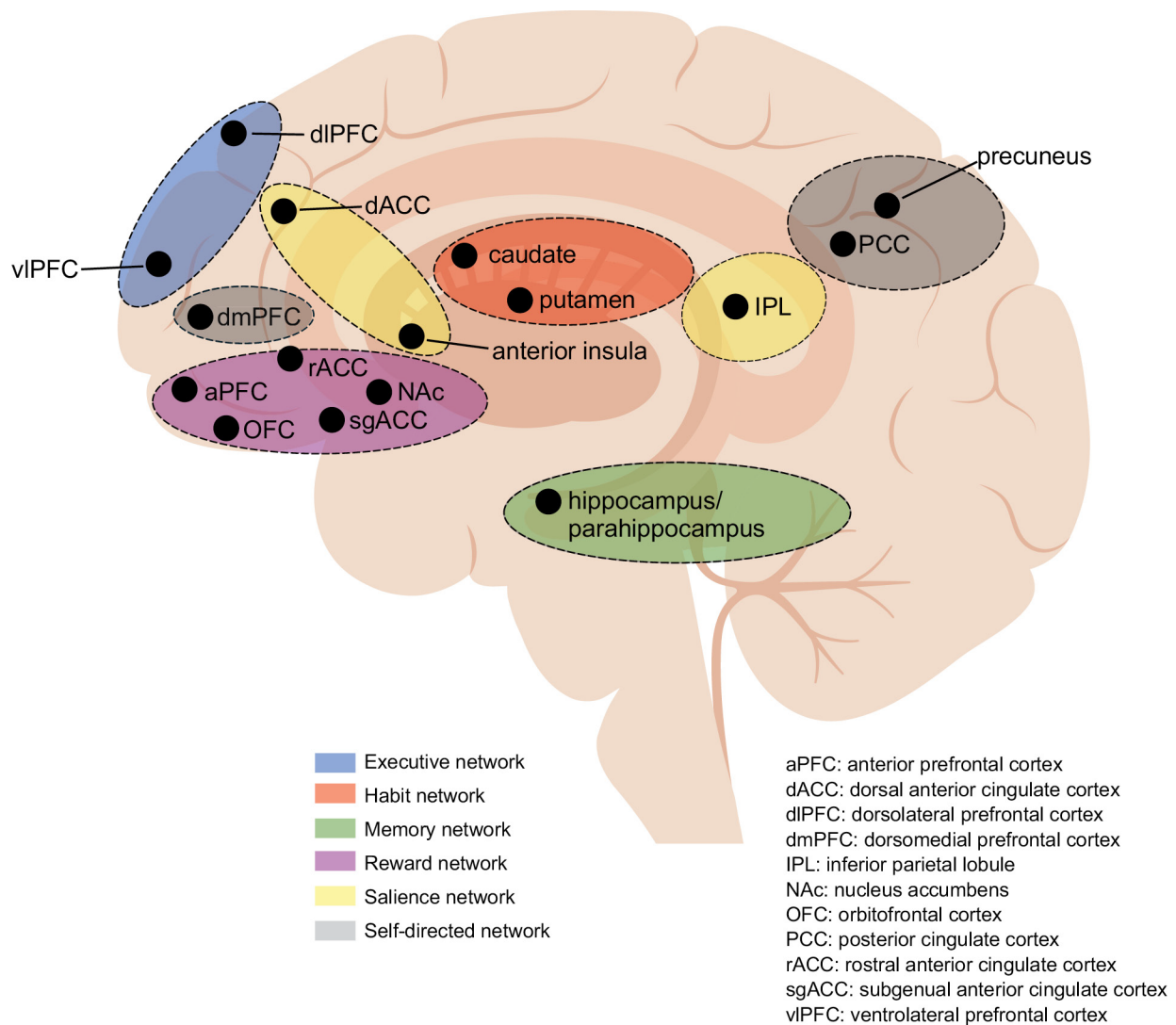
Neuronal nicotinic acetylcholine receptors (nAChRs) play a key role in mediating the interactions of nicotine and ethanol.^{6,36,70} nAChRs are widely expressed throughout the brain and are present on many of the key neuronal projections from the ventral tegmental area depicted in Figure 6.2. Nicotine directly binds to nAChRs in the brain, while alcohol modulates these receptors both directly, by interacting with them, and indirectly, by influencing other signaling pathways that affect nAChR function.^{71,72} Nicotine stimulates the cholinergic system and the nAChRs specifically in the ventral tegmental area.^{36,73} This stimulates the release of dopamine into the nucleus accumbens and augments activity in the prefrontal cortex. Therefore, nicotine can act to prime dopamine neurons in the ventral tegmental area such that alcohol becomes more reinforcing. Animal studies have also shown that consumption of ethanol alone leads to increases in dopamine release in the nucleus accumbens via activation of nAChRs in the ventral tegmental area, which contributes to the reinforcing properties of alcohol.^{71,73,74} Thus, co-use of nicotine and ethanol produces greater reinforcement through synergistic dopamine effects, which then causes continued self-administration of both substances.^{52,73}

The interaction effects of nicotine and ethanol highlight that responses to these substances can be enhanced with co-use and will change over time with continued use. Continued use and co-use may lead to the development of tolerance, especially if use increases. nAChRs are also highly expressed in the medial habenula and IPN (Figure 6.2), two regions believed to be involved in abstinence and withdrawal, but this circuit is not as well-characterized as the mesolimbic pathway.^{75,76}

Neuroimaging Studies

A longstanding question in the neurobiology of addiction has been whether early baseline differences in brain structure and function contribute to the development of substance use disorders and/or whether substance use leads to lasting changes in brain structure, brain function, or both. As of 2026, however, it has not been feasible to unpack substance-use-related differences in brain structure or function, because most participants in past neuroimaging studies have been adults.⁷⁷ With time, answers to this important question may come from 2, large-scale longitudinal neuroimaging studies ongoing as of 2026: the HBCD study, which began enrolling pregnant participants in 2023,^{78,79} and the ABCD study which began enrolling 9–10 year olds in 2016.^{31,32} Additionally, although preclinical neuroimaging studies in animal models have given insight into the direct consequences of chronic drug use,⁸⁰ the complex interactions between genetic vulnerability factors and chronic substance use in humans cannot be sufficiently modeled in animals. Neuroimaging studies in humans have attempted to incorporate underlying genetic risk factors into studies of brain structure and function; until recently these have been limited mainly to candidate genes and small sample sizes.⁸¹ These studies share similar design constraints as the original candidate gene studies. Nevertheless, neuroimaging techniques have been used to study the three major neurocircuits implicated in substance use disorder: the (1) basal ganglia, (2) extended amygdala, and (3) prefrontal cortex.⁴¹ The most comprehensive review (published in 2018) of the neuroimaging literature in adults with substance use disorders has extended this prior theoretical framework by identifying 6 large-scale brain networks consistently implicated in addiction (Figure 6.3).⁸²

- The reward network includes subcortical and cortical brain regions activated during the appraisal of subjective value (anterior prefrontal cortex, rostral anterior cingulate, nucleus accumbens, orbitofrontal cortex, and subgenual anterior cingulate).
- The striatal habit network underlies learning of automatized behavior (caudate and putamen).
- The salience network is involved in (re)directing attentional resources toward salient stimuli (dorsal anterior cingulate, anterior insula, and inferior parietal lobule).
- The executive network supports the selection of possible behavioral responses (dorsolateral prefrontal cortex and ventrolateral prefrontal cortex).
- The self-directed network is activated during self-directed/referential cognitive processes (precuneus, posterior cingulate cortex, and dorsomedial prefrontal cortex).
- The memory network is involved in flexible, multi-cue learning and memory (hippocampus and parahippocampus).

Figure 6.3 Large-Scale Brain Networks Implicated in Addiction Through Neuroimaging

Source: Adapted from Zilverstand et al. 2018.⁸²

Importantly, Zilverstand and colleagues (2018)⁸² noted that multiple studies have revealed the importance of emotional and cognitive factors beyond the feelings of anticipation, intoxication, and withdrawal described in the classic triadic model of addiction. Overall, the evidence from human neuroimaging studies supports the role of impaired salience attribution, negative emotional states, and dysregulated executive function underlying substance use disorders, but also points to the importance of changed appraisal of subjective value, altered self-directed processing, and changes in flexible learning and memory.⁸² These higher-order cognitive processes could not be studied in the animal models from which the classic triadic model of addiction was mostly derived; hence, their importance was only revealed through the human neuroimaging literature. Furthermore, Zilverstand and colleagues' review of the neuroimaging literature highlighted that, for individuals with substance use disorders, both the classically studied and the newly identified brain networks show increased recruitment during

substance-related processing. However, they are not activated to the same degree during non-substance-related processing, when individuals with substance use disorders engage in non-drug-related processing.⁸² Finally, the neuroimaging literature points to nuanced sex differences in the neurobiological mechanisms underlying substance use disorders,⁸³ though this remains an area of need for further research.

It is important to recognize that the networks described in the human neuroimaging literature are slightly different than the pathways described in the literature based on animal models.⁸⁴ This occurs because neuroimaging studies use a whole-brain approach to measure neuronal activation in humans *in vivo*, rather than the localized measurements in animals following experimental procedures. Although the same or similar brain regions are examined, they are therefore sometimes described at different levels of detail, depending on the tools used to measure substance effects, resulting in somewhat different descriptions of the role of specific regions. There may also be differences between species in relevant pathways and networks.

Several studies have used neuroimaging to examine changes in the brain associated with nicotine or ethanol, but very few studies have considered both substances together.⁸² In 2014, Liu and colleagues⁸⁵ used functional magnetic resonance imaging (fMRI) to examine brain regions activated in response to cues for smoking and alcohol use. The study used a framework of three networks (reward, salience, and cognitive control). Their data supported an interconnection between networks that activated together in response to both smoking and alcohol cues. Specifically, they found that the posterior cingulate cortex and right posterior insula were associated with alcohol behavioral traits (loss of behavioral control) and responded to both smoking and alcohol cues. These two regions were classified as part of the salience network in this study,⁸⁵ whereas Zilverstand and colleagues placed the posterior singular cortex in the self-directed network and the insula in the salience network.⁸² However, there were also regions that showed differences in response to alcohol taste cues versus tobacco visual use cues.

Multiple studies have also examined volumes of various brain regions associated with cigarette smoking and alcohol use.⁸⁶⁻⁸⁸ A 2020 mega-analysis (meta-analysis of pooled data from multiple existing datasets) revealed different results for individuals with alcohol dependence and smoking compared with nondependent controls.⁸⁷ Smaller volumes in the hippocampus, thalamus, putamen, and amygdala were detected among individuals with alcohol dependence. However, compared with nonsmoking control participants, larger volumes in multiple regions, including the hippocampus and right nucleus accumbens, were associated with smoking. It was unclear whether these differences were the result of substance exposure and continued use, or whether individuals with early differences in brain structure were at increased risk for the development of dependence and substance use disorders.

Two developments have opened the neuroimaging studies to more powerful analyses: (1) large scale datasets with tens of thousands of subjects and (2) Mendelian randomization, that can use genetic variation to help determine whether an exposure is causally related to an endpoint (see chapter 5). A 2022 Mendelian randomization study addressed this predisposition or consequence question by using subcortical brain volume data from approximately 37,000 participants in combination with tobacco and alcohol phenotypic and genotypic data from the UK Biobank study.⁸⁹ Alcohol dependence was inversely associated with volume of the amygdala and hippocampus; similarly, cigarettes per day was inversely associated with

hippocampal volume. The study authors did not perform a combined analysis to examine comorbid effects. The results strongly suggest that differences in brain volume are the consequence of use, rather than a predisposing factor. As genetically informative neuroimaging datasets continue to emerge, further knowledge will be gained of the predisposing features in the brain that increase tobacco and alcohol use and the consequences of substance use.

More research is moving beyond the addiction cycle to try to understand different trajectories leading to addiction and the functional domains associated with substance use. For example, detailed phenotyping of a sample of 454 adults in the United States, 186 with current alcohol use disorder, identified 3 neurofunctional domains—incentive salience, negative emotionality, and executive function—that distinguished between participants with and without alcohol use disorder.⁹⁰ Drossel and colleagues (2023)⁹¹ characterized neurobehavioral subtypes based on extensive questionnaires for 173 people with past substance use disorders and 420 controls. Among people with a past substance use disorder, latent profile analysis identified three subtypes involving higher approach-related behavior, lower executive function, or higher negative emotionality. Participants in these three groups had distinct patterns of functional connectivity between brain networks, as measured with fMRI, that were associated with return to substance use. These results suggest substantial heterogeneity in these three major mechanisms related to addiction. Additionally, these results point towards the existence of stable trait-like factors related to dependence and addiction.

Shared Genetic Factors That Contribute to Tobacco and Alcohol Behaviors

This section is divided into three parts: (1) background information about methodology for the study of genetics of complex traits, (2) a description of the challenges of combining data from studies that used different measures of tobacco and alcohol related phenotypes, and (3) a summary of findings from large GWAS. As discussed in the introduction of this chapter, tobacco and alcohol use involve a complex developmental trajectory and diverse phenotypes beyond simply “use” or “substance use disorder.” This section emphasizes that there are multiple behaviors associated with tobacco and alcohol use and better understanding and measurement of these behaviors in genetic studies could strengthen understanding of these complex traits. In many studies, researchers have focused on tobacco or alcohol behaviors individually, although in most cases the participants were assessed for multiple substances, and many used both tobacco and alcohol (see Appendix 6A). Technological advancements and the development of innovative analytical approaches have bolstered the ability to perform integrative analyses that ask more nuanced questions about shared genetic features relevant to both tobacco and alcohol across the lifespan. In humans, most studies of the genetics of tobacco use have examined cigarette smoking; however, genetic studies in animal models have also examined the effects of nicotine specifically.⁸ With changes in the tobacco marketplace and the increasing use of e-cigarettes and other novel tobacco products (see chapter 2), current and future genetic studies may consider addressing tobacco use other than cigarette smoking.

How Genetic Studies Are Conducted

As mentioned above, considerable evidence from genetic studies has demonstrated that tobacco and alcohol use disorders, as well as other substance use disorders and psychiatric disorders, have both shared and unique genetic risk factors.¹⁻⁷ Geneticists use twin and family study designs to estimate the proportion of variance in a trait that is due to genetic factors and the proportion that is due to environmental factors.⁹²⁻⁹⁴ Because monozygotic (identical) twins share 100% of their genes, while dizygotic (fraternal) twins share on average only 50%, heritability can be estimated by comparing the similarity of an observed trait between monozygotic and dizygotic twins. Heritability is a statistical concept that estimates how well differences in genetic factors within a population account for differences in a particular trait (phenotype). Heritability can range from zero to one, where values close to zero indicate that the trait is due mostly to environmental factors in the population studied. Higher heritability estimates suggest a larger proportion of variation in the trait within that population is due to genetic factors, which can include both additive and multiplicative effects between genes.⁹²⁻⁹⁴ The remaining phenotypic variance due to environmental factors can be parsed into those shared between siblings reared together and nonshared environmental factors unique to each person.

Heritability is dependent on the population in which it is studied, and heritability can change over time with different environments as well as with changes in the genetic makeup of a population, for example through genetic admixture.⁹²⁻⁹⁴ Twin and family studies are usually underpowered to detect sex-dependent differences in heritability but can provide evidence of potential differences.⁹⁵

It is also important to distinguish heritability from other similar concepts.⁹²⁻⁹⁴

- Heritability does not indicate the proportion of phenotypic variability determined by genetics for any particular person. For example, a heritability estimate of 50% for the trait “number of cigarettes smoked per day,” indicates that approximately half of the variability in that population for this trait is due to genetic differences in that population at that time.
- Heritability estimates do not provide any information about the specific genetic or environmental factors contributing to a trait. Heritable traits are not the same as familial traits. Familial traits are traits shared within a family. They may or may not include a genetic component.
- Heritability estimates are not intended to indicate that a trait cannot be changed. Genes are not destiny. For instance, although the risk of developing certain chronic conditions like type 2 diabetes has a genetic component, behavioral factors such as diet and physical activity play a significant role in disease development. A person with a genetic predisposition to diabetes can significantly reduce their risk through healthy behaviors, demonstrating that genetic risk can, in many cases, be mitigated by environmental factors.

Heritability is used by geneticists as an important first step to confirm that a trait is determined in part by genetic factors, and it is also used to determine how much shared genetic variance exists between traits.

Decades of research demonstrate that, across populations, an approximately equal split between genetic and environmental factors contributes to risk for smoking and alcohol use.^{10,96} A 2003 meta-analysis of twin studies from the United States, Australia, and Finland provided heritability estimates and shared and non-shared environmental risk factors for smoking initiation and cigarette smoking for men and women.⁹⁷ For both sexes and both phenotypes, heritability estimates centered around 50%,⁹⁷ as is the case for most substance use behaviors.⁹⁸ A similar meta-analysis of alcohol use disorders from 12 twin and 5 adoption studies revealed a heritability estimate of 49% for alcohol use disorder, with no differences due to sex.⁹⁶ Furthermore, two studies modeling rate of progression to alcohol use disorder suggested that environmental factors played a larger role in initiation of alcohol use, while genetic factors contributed more toward continued use and increased use.^{99,100} Some of the underlying environmental variables were associated with family circumstances that may have genetic influences, as well. Cohort studies addressing the ontogeny of substance use could help clarify the relative importance of genetic and environmental factors for initiation and use.^{79,101} Notably, environmental factors, such as social influences of parental or peer smoking behavior and attitudes, also appear to play a larger role in smoking initiation than genetic factors.^{102,103}

Twin studies examining shared genetics of substance use disorder generally and for specific substances, including tobacco and alcohol, suggest a complex mix of genetic and environmental influences that may differ for different substances.¹⁰⁴ Delineating the relative contributions of each is a substantial methodological challenge, especially as many past studies suggest that other factors, such as disinhibition, are shared across many substance use disorders and other comorbid psychiatric diseases. This is discussed in detail in NCI Monograph 20.⁸

As reviewed by Goldman and colleagues (2005),¹⁰⁵ initial studies investigating the genetic contributions to alcohol and tobacco use were conducted either as family-based linkage analyses or as case-control association studies of unrelated individuals.^{10,106} Linkage studies examine genetic markers spread across the entire genome in families to identify regions of the genome shared by family members affected by a trait of interest, called quantitative trait loci. This approach had notable successes, for example identifying the genetic basis of single-gene disorders, such as cystic fibrosis and Huntington's disease.¹⁰⁷ Genetic loci for some substance use behaviors were identified through this approach, including identification and confirmation of alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH2*) genes as loci affecting alcohol use behaviors (see chapter 5). However, in general, linkage studies failed to identify strong loci linked to tobacco and other substances.¹⁰⁵ Rather, behavioral traits are largely influenced by the small effects of thousands of genetic factors in combination with environmental influences.¹⁰⁵

An alternate approach was common until the early 2000s, whereby case-control studies compared unrelated individuals with a specific characteristic, trait of interest, or disease (cases) with unrelated individuals without that characteristic (controls).¹⁰ Investigators would then use these studies to compare the frequency of hypothesized candidate genetic variants in the cases and controls. For studies of substance use disorders, these “candidate gene” studies often focus

on genes expressed in neuronal pathways known to be involved in dependence and addiction, such as serotonin receptor and dopamine transporter, among others.¹⁰⁸ However, these studies had numerous limitations, including being underpowered to detect small effect sizes,¹⁰⁹ not always controlling for population stratification (a situation in which cases and controls are derived from genetically distinct underlying populations with different frequencies of specific genetic variants),¹¹⁰ and often not thoroughly considering the impact of multiple testing on statistical significance.^{108,111-115} Reflecting these limitations, results from these initial studies largely failed to replicate in later GWAS studies that appropriately considered potential population stratification and multiple comparisons.^{108,111-114}

In the early 2000s, high-throughput genotyping technologies emerged that facilitated assessment of many thousands of variants across the genome, leading to the advent of GWAS.¹¹⁶⁻¹¹⁸ This moved the field away from family-based linkage studies toward case-control association studies with sufficiently large sample sizes to detect small effects of single nucleotide polymorphisms (SNPs), the most commonly assessed genetic variant. Although GWAS provide benefits over linkage studies and have now yielded thousands of genetic variants associated with tobacco and alcohol use,^{1,2} many GWAS to-date have had other limitations, including limited phenotypic assessments, challenges with controlling for population stratification, and samples collected primarily from participants of European ancestry.^{110,116,118} Efforts toward more detailed phenotypic assessments and increased collection of samples with individuals from diverse ancestry have begun to address these limitations.¹¹⁶ In addition, initial studies (linkage, candidate gene, and GWAS) typically focused on either smoking or alcohol phenotypes individually.¹¹⁹ As additional studies have examined co-use, the field has begun to learn more about shared molecular genetic factors.

Challenges in Conducting Phenotype Assessments

There are several challenges associated with assessing substance use phenotypes for genetic, physiologic, and behavior studies. Many large-scale studies of tobacco and alcohol use are meta-analyses of samples collected from existing studies in which the phenotypic measures often do not align perfectly (see Table 6.1 and Appendix 6A). For example, the assessment protocols used often vary across the studies included in a meta-analysis, so a significant amount of time must be devoted to harmonizing the phenotype before results can be pooled. Resources with recommended measures for cohort and genetic studies (e.g., the PhenX Toolkit) are available and useful for incorporating in various types of studies. Further, previous research is limited by lack of ancestral diversity that limits the generalizability of genetic findings and their relationship to phenotypic diversity and the ability to implement precision medicine across all populations.¹²⁰

In addition, as discussed previously, findings from earlier genetic studies have not been replicated in larger studies. GWAS efforts are often subject to data sharing policies that require scientific data to be available for use by the larger research community.^{121,122} Such data sharing requirements are vital to ensure reproducibility and rigor of analyses performed using the data. Despite progress in standardizing data, expanding biobanks, and promoting data sharing, challenges such as inconsistent measures and lack of diverse representation still affect the overall impact and applicability of genetic research.

Measurement challenges also contribute to important limitations in large-scale genetic studies of substance use. In general, measures for smoking have involved variables describing initiation and lifetime patterns of use, such as age of initiation, number of cigarettes smoked per day, and smoking cessation (see chapter 2). Each of these variables may be defined in different ways, depending on choices made in the underlying study and evolving evidence for the validity and reliability of different instruments. Large-scale studies typically do not include diagnostic measures of tobacco use disorder.¹³ Furthermore, specific diagnostic criteria for substance use disorder from the Diagnostic and Statistical Manual of Mental Disorders (DSM) continue to evolve.^{123,124} Other measures of tobacco use are also used and many studies have measured nicotine dependence with the Fagerstrom Test for Nicotine Dependence (FTND).^{125,126}

For alcohol behaviors, many of the initial large-scale studies were limited to queries measuring the number of alcohol-containing drinks consumed per week.¹²⁷ Some studies have begun to disentangle similar and different genetic results for consumption measures compared to measures of an alcohol use disorder, such as the Alcohol Use Disorders Identification Test (AUDIT),¹²⁸ developed by the World Health Organization.¹²⁹ A 2023 cross-ancestry meta-analysis that measured alcohol consumption and alcohol use disorder in the same participants and focused on those who reported current drinking found that the genetic correlation between alcohol use disorder and alcohol consumption is quite high in both European (0.86–0.92) and African (0.98–1.00) ancestry groups.¹³⁰ This reflects a very large proportion of variance that is likely due to pleiotropy (one or more genes influencing two traits) and confirms that there are multiple loci relevant both to alcohol consumption and alcohol use disorder. However, Kember and colleagues¹³⁰ also identified a set of variants related to alcohol use disorder, independent of level of alcohol consumption; such variants are of great interest in better understanding the transition to alcohol use disorder and its harmful consequences.

In studies focused on alcohol and other substances, DSM diagnoses of substance use disorder have been examined.¹²⁸ In addition, the inclusion of phenotypes that are not defined as disorders, such as presence or absence of alcohol consumption, increases the sample size available for GWAS analysis, thereby increasing power to detect genes associated with alcohol-related behavior.¹³¹ Most initial studies of the genetics of tobacco and alcohol use examined results individually for smoking and alcohol consumption, followed by a simple comparison of overlapping genes.¹³² It has also been common for investigators to analyze data for other substances and/or psychiatric disorders in combination with tobacco and alcohol.¹¹⁹ In 2018, a new method for multi-trait analysis of GWAS (MTAG) was developed to enable joint analysis of multiple traits, which boosts statistical power for detecting associations with each trait.¹³³ MTAG can be applied to GWAS summary statistics without access to individual-level data for multiple traits, and the summary statistics do not need to come from independent discovery samples. For each SNP, trait-specific effects are estimated in a computationally efficient manner.¹³³ Examples of application of this tool for tobacco and alcohol phenotypes are presented later in the chapter.

Another challenge associated with assessment of tobacco and alcohol use is that overall study design can affect results obtained. Study design includes decisions about participant inclusion criteria such as age, sex, ancestry, measures of socioeconomic status, and others that may or may

not be clearly described. For tobacco and alcohol use, it can also be important to define thresholds of exposure. Initiation and experimentation as behaviors themselves may be more closely related to environmental variables such as access to these substances or social context, but the family setting and individual risk-taking also involve traits influenced by genetics and genotype by environment interactions.¹³⁴ Not everyone who tries tobacco or alcohol progresses to regular smoking or drinking. To address the idea that a person with very limited experience with a substance may not be considered as having initiated use, some studies define a threshold of use, such as having smoked at least 100 cigarettes for an adult participant to be considered a person who has ever smoked.^{135,136} Changes in availability and use of specific tobacco products are another important point to consider when studying smoking behaviors. Although cigarette smoking initiation has decreased substantially, the introduction of e-cigarettes in the mid-2000s has led to substantial uptake among adolescents. Since 2014, e-cigarettes have been the most used tobacco product among adolescents, and adolescent e-cigarette use remains a major public health problem.^{137,138} As of 2026, there is no standard for a minimum threshold of e-cigarettes or alcohol exposure for classifying participants as having ever used e-cigarettes or alcohol. Such a standard will be helpful, because having taken a puff of an e-cigarette or a single sip of alcohol does not adequately classify an individual as having initiated use. Furthermore, there is a lack of research on whether a combined threshold might be useful when examining both tobacco and alcohol use and the genetic correlates of nondaily tobacco and alcohol use.

Main Results From Genetic Studies

This section presents findings from genetic studies that emerged during the early 2000s through 2025. At the individual gene level, early studies identified associations with genes involved in the metabolism of nicotine and ethanol and genes associated with known targets of nicotine, nAChRs, in the brain. Subsequent large-scale studies expanded the number of variants and genes associated with smoking and alcohol use to the thousands, so interpreting the results has become much more challenging. Researchers developed methods to determine whether genes fall within specific physiological pathways, cell types, or other shared biological features to better understand the mechanistic pathways associated with specific genes. Although initial analytical approaches were primarily focused on a single phenotype, the development of multi-trait analysis has proven effective at increasing the number of variants associated with tobacco and alcohol use. As samples including individuals from more diverse ancestries have continued to grow, it has become clear that similar genetic pathways contribute to risk for tobacco and alcohol use disorders across populations.

Drug Metabolism and Neuronal Response Genes

Initial genetic results for both nicotine and ethanol have highlighted the impact of individual differences in drug metabolism on use and use disorders. The first genes identified that influence alcohol use, albeit somewhat indirectly, were the *ADH* and *ALDH2* genes,¹³⁹ which encode the proteins that are the main enzymes that metabolize ethanol and its primary metabolite, acetaldehyde (see chapters 4 and 5). Similarly, variants within genes coding for proteins that metabolize nicotine (cytochrome P450 and *CYP* genes) have been reproducibly associated with smoking behaviors.^{140,141} Another highly replicated association with smoking involves nAChRs (*CHRN* genes).¹⁴² This region includes the top genome-wide significant associated genes for

smoking behaviors^{26,136} and also lung cancer (see chapter 5)^{26,136} and has effectively become a positive control for human genetic studies related to nicotine phenotypes. These initial studies were described in both the 2010 Surgeon General's report and NCI Monograph 20.^{8,10} nAChRs are the main site of action for nicotine in the brain, indicating that these genetic findings align well with the neurophysiology of nicotine's action.

Further characterization of the *CHRNA5/CHRNA3/CHRNA4* gene region revealed multiple independent genetic signals within this cluster, perhaps implicating functional variants in nearby genes as well.¹⁴³ However, the primary genetic variant, a single nucleotide polymorphism, rs16969968, corresponds to an amino acid change in the *CHRNA5*, a gene coding region that has been demonstrated to confer differential functional responses in the nAChRs.¹⁴⁴ Other genetic signals in the region are also associated with differential gene expression.¹⁴⁵ Evidence for an association between *CHRN* genes and alcohol behaviors specifically is equivocal as the large-scale human GWAS have not replicated findings from candidate gene studies, which have found associations between various subunit genes and alcohol behaviors.¹⁴⁶⁻¹⁴⁹ Regardless, findings of the association have informed the use of varenicline, a high-affinity partial agonist at $\alpha4\beta2$ nAChRs, as one of the current treatments for smoking.¹⁵⁰

Some studies have reported associations between variation at SNP rs16969968 in the *CHRNA5* gene and a variety of differences in brain structure using neuroimaging approaches.¹⁵¹ Many of these appear as baseline differences, independent of whether someone smokes, and there has been some evidence for differential effects of smoking dependent on genotype, along with evidence for differential cue reactivity by sex.¹⁵¹ However, these studies had several design limitations (small sample size and differences in age, location, cohort, possible population stratification, or other environmental confounders), so it will be important to replicate the studies in larger samples before drawing firm conclusions. Genetic associations in humans between different *CHRN* genes and alcohol behaviors have been difficult to disentangle from the associations with smoking behaviors. A possible explanation for these difficulties is the high levels of co-use of these substances (see chapters 2 and 3).⁶ New analyses or studies of people who use cigarettes or alcohol exclusively could help address this challenge.

Genome-Wide Association Studies

Appendix 6A presents a summary of selected large GWAS for tobacco, alcohol, tobacco and alcohol combined, tobacco and alcohol with other substances, and imaging studies published since 2018, with information about the studies' samples and main results. The search strategy for identifying relevant large GWAS is summarized in Appendix 6B. Four publications focusing specifically on tobacco, alcohol, and combined effects results are summarized in this section and in Table 6.1. The first publication discussed in this section presented results from the most powerful study conducted as of 2026, GWAS and Sequencing Consortium of Alcohol and Nicotine use 2 (GSCAN2), which included approximately 3.4 million individuals from 60 cohorts representing people with biological ancestors from African, American, East Asian, and European populations, with around 21% of the total sample derived from non-European samples.² This publication reported genetic loci associated with individual smoking and alcohol

phenotypes,² whereas the second publication conducted a multi-trait analysis for a combined addiction risk factor including four substances: alcohol, tobacco, opioids, and cannabis.⁴ Two other publications applied MTAG to conduct joint analyses of genetically correlated traits. One of these studies focused on smoking and alcohol use phenotypes only,¹¹ while the other included smoking, alcohol, opioids, and cannabis.¹⁴ All four studies have begun to converge on loci shared across substances.

Table 6.1 Key Genome-Wide Association Studies of Tobacco and Alcohol

Study	Phenotype(s)	Sample ^a	Selected results
Cheng et al. 2023 ¹¹	Alcohol and smoking joint analysis	Million Veteran Program • <i>N</i> = 318,694 European American subjects from Million Veteran Program database	• Joint analysis of alcohol use measures and smoking measures using MTAG ▪ 21 loci for smoking initiation and 17 for smoking cessation when combined with alcohol use disorder (compared to 16 and 8, for single-trait smoking initiation or cessation, respectively) ▪ 10 shared loci for alcohol use disorder and smoking status, including <i>SIX3</i>, <i>NCAM1</i>, and near <i>DRD2</i> • MTAG of smoking behaviors with alcohol consumption did not enhance discovery
Hatoum et al. 2023 ⁴	Alcohol Cancer Tobacco Opioid Cannabis General addiction risk factor	• <i>n</i> = 1,025,550 European American subjects and <i>n</i> = 92,630 African American subjects	• Disaggregated general and substance-specific loci; substance-specific loci include metabolic and receptor genes ▪ 19 addiction risk factor SNPs ▪ 9 alcohol-specific ▪ 32 tobacco-specific ▪ 5 cannabis-specific ▪ 1 opioid-specific
Saunders et al. 2022 ²	Alcohol Smoking	• GSCAN2: <i>N</i> = 3.4 million individuals from 4 major clines of global ancestry (~21% non-European)	• Many of the 3,823 associated variants from 2,143 loci showed consistent effect sizes across ancestry dimensions ▪ Polygenic scores developed in one ancestry performed poorly in others

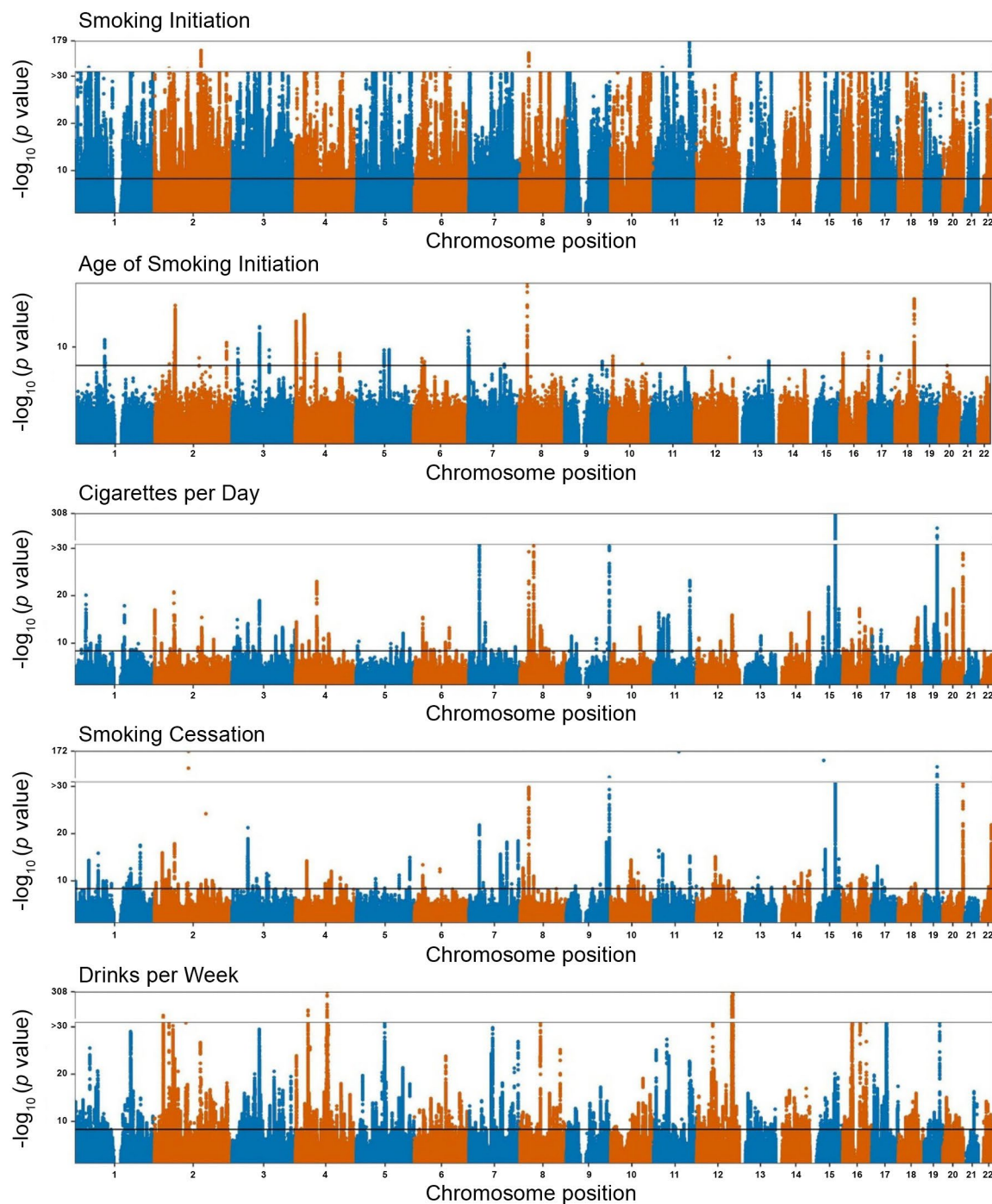
Table 6.1 (continued)

Study	Phenotype(s)	Sample ^a	Selected results
Xu et al. 2023 ¹⁴	Opioid Cannabis Alcohol Smoking	Yale-Penn sample ($n = 5,692$ European ancestry, $n = 4,918$ African ancestry); Penn Medicine Biobank sample ($n = 29,054$ European ancestry, $n = 10,265$ African ancestry)	- Multi-trait analysis of opioid use disorder, cannabis use disorder, alcohol use disorder, and smoking initiation in European ancestry individuals; examined opioid use disorder, alcohol use disorder, and smoking trajectory in African ancestry individuals - MTAG boosted number of loci identified for all traits and identified genes not previously linked to any substance, and increased power of polygenic scores - European ancestry results: 36 loci for opioid use disorder, 60 loci for cannabis use disorder, 52 loci for alcohol use disorder, 144 loci for smoking initiation - African ancestry results: 2 loci for opioid use disorder, 3 loci for alcohol use disorder, 1 locus for smoking trajectory

Note. GSCAN2 = GWAS and Sequencing Consortium of Alcohol and Nicotine use 2; MTAG = multi-trait analysis of GWAS; SNP = single nucleotide polymorphism.

^aPopulation descriptors (e.g., European American) are quoted from the cited studies.

Large Genome-Wide Association Study for Tobacco and Alcohol. In GSCAN2, a large GWAS study, investigators examined four cigarette smoking phenotypes: initiation (whether an individual ever smoked regularly), the age of onset of regular use (age individual began smoking regularly), amount smoked (cigarettes per day among people who currently or formerly smoked), and cessation (current versus former smoking).² “Regular” use was based on survey questions addressing regular use explicitly or questions about number of cigarettes smoked over the life course or smoking every day for at least 1 month.² One alcohol use phenotype, drinks per week, was available across most studies. The results of this study are illustrated in Figure 6.4 using Manhattan plots, which allow graphical representations of the results of GWAS.¹⁵² In these plots, the x-axis displays the genomic location of the SNPs identified and the y-axis the negative base 10 log of the p value obtained for each SNP. Points above the solid black line represent variants that have a significant association with the phenotype of interest adjusting for the genome-wide comparison number. Some of the y-axes are discontinuous because of very low p values for some SNPs (e.g., 1.9×10^{-308} for some drinks per week SNPs).² Compared to the original GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) publication,¹ the multiancestry analysis greatly expanded the number of loci found, identifying a total of 2,143 loci across all phenotypes, with 3,823 independent variants.² Follow-up analysis of high-priority genes nearby top loci revealed that these genes were highly enriched across brain and nerve tissues, specifically within regions of the cortex, hippocampus, amygdala, hypothalamus, and midbrain. Furthermore, the high-priority genes were enriched in gene pathways related to neurogenesis, neuronal development, neuronal differentiation, and synaptic function, connecting them to the developmental and longitudinal aspects of tobacco and alcohol use disorders.² Five loci were associated with all 4 smoking phenotypes and the alcohol phenotype, localizing to large regions on chromosomes 2, 8, and 16, all of which contain multiple genes (G. Saunders, Ph.D., personal communication, September 12, 2023). These areas are excellent targets for focused attention on the comorbidity between tobacco and alcohol use.

Figure 6.4 Multiancestry Meta-Analysis Manhattan Plots for Smoking Behaviors and Alcohol Consumption

Note. Each dot on the plot signifies a single nucleotide polymorphism (SNP). Genomic coordinates are displayed along the x-axis, and each color block represents a chromosome. The y-axis is the negative logarithm of the association p value for each SNP. The strongest associations have the smallest p values (e.g., 10^{-15}), and their negative logarithms will be the greatest (e.g., 15). The black line across the plot marks 5×10^{-9} and SNPs above this line surpass the genome-wide significance level. Some y-axis scales are discontinuous to illustrate variants with very small p values.

Source: Saunders et al. 2022.² Reproduced, with minor formatting changes, [with permission](#) from *Nature*.

Multi-Trait Genome-Wide Association Studies. The Psychiatric Genomics Consortium (PGC) was established to unify researchers studying the genetic basis of psychiatric disorders and consists of more than 800 investigators from 36 countries with combined datasets exceeding 400,000 participants.¹⁵³ The Substance Use Disorder Working Group of PGC is focused on examining the genetics of substance use disorders and comorbid phenotypes.¹⁵⁴ Hatoum and colleagues (2023)⁴ conducted a multivariate GWAS meta-analysis of a “general addiction risk factor,” alongside analysis of individual substances including “problematic alcohol use,” “problematic tobacco use,” opioid use disorder, and cannabis use disorder. The term “problematic substance use” was introduced when one or more of the measures in the meta-analysis was derived from a scale rather than a diagnostic measure (A. Hatoum, Ph.D., personal communication, March 19, 2024). Hatoum and colleagues defined “problematic alcohol use” as including both alcohol use disorder (as a case-control GWAS) and the Alcohol Use Disorders Identification Test-Problem Items (AUDIT-P) subscale, a continuous measure that focuses on the problematic consequences of drinking. “Problematic tobacco use” was quantified based on the FTND scale of dependence.¹²⁵ The FTND has a genetic correlation of 0.95 to 0.97 with cigarettes per day, so these 2 items were parceled together using MTAG (A. Hatoum, Ph.D., personal communication, March 19, 2024). The total sample size included 1,025,500 individuals of European ancestry and 92,630 individuals of African ancestry.⁴ In the European ancestry sample, the study identified 19 independent SNPs associated with the “general addiction risk factor” and highlighted top associations with the *PDE4B* and *DRD2* genes, both of which are involved in the dopaminergic reward pathway. Importantly, the association with *DRD2* was discovered through chromatin remodeling analyses, which indicates the variants are likely to be involved in regulation of the gene by turning it on or off under different circumstances (e.g., during development, time of day, in response to an environmental stimulus). This is a common theme among GWAS results, where many of the top SNPs do not fall within protein-coding regions of genes, but rather in regions where function is more difficult to predict.¹⁵⁵ In these cases, the SNP could be in a region contributing to regulation of gene expression or it could be associated (in linkage disequilibrium) with a different, causally related SNP.

Hatoum and colleagues (2023)⁴ observed that substance-specific loci fell into three categories: substance receptors, substance-specific metabolism, and general neurotransmitter mechanisms. The first two categories confirmed previous results for both tobacco (e.g., *CHRNA5*) and alcohol (e.g., *ADH1B*). The largest category of variants was associated with general neurotransmitter mechanisms. Hatoum and colleagues also presented tables listing the top SNPs from each chromosome; in many cases, they are associated with both “problematic tobacco use” and “problematic alcohol use.”

Finally, Hatoum and colleagues⁴ showed that the polygenic score generated based on their results and applied in an independent sample of mostly substance-naïve children ages 9–10 years (from the ABCD study)²⁵ was correlated with other co-occurring earlier childhood behaviors and environments, including measures of externalizing behavior and fun-seeking, sleep duration, parental externalizing and substance use behaviors, and socioeconomic disadvantage.⁴ While a number of these associations are statistically significant, the standardized effect estimates were small, ranging from about 0.06 to 0.10.

This genetic connection to early risk factors highlights that predecessors of substance use are in part genetically driven by the same genetic variants associated with later tobacco and alcohol use. As with providing genetic risk information about other diseases or medical conditions, providing genetic risk scores for tobacco and alcohol use must be done with great care because this information can be stigmatizing or result in inappropriate victim blaming. This is especially challenging when treatments are only modestly effective and when social and environmental factors influencing tobacco and alcohol use are often difficult to address. The emerging body of research addressing how people respond to biological or genetic models of behavior and how such framing relates to stigmatization may be informative.¹⁵⁶ As of 2026, evidence is mixed as to whether information about genetic risk influences behavior change.¹⁵⁷ Furthermore, there appear to be geographic and cultural differences in how people respond to information about family and genetic variation in risk.¹⁵⁶ Continued research is needed to optimize communication about genetics and environmental aspects of risk.

Two other publications have applied MTAG to the analysis of genetically correlated traits. This approach was applied to data from the Million Veteran Program ($N = 318,694$) to examine 2 smoking phenotypes (smoking initiation and smoking cessation) and 2 alcohol phenotypes (alcohol consumption, as defined by the Alcohol Use Disorders Identification Test-Concise [AUDIT-C], and alcohol use disorder).¹¹ For both smoking initiation and smoking cessation, the MTAG strategy using alcohol use disorder GWAS summary statistics identified more genome-wide significant loci than the initial single-trait analysis.¹¹ In contrast, no additional variants were discovered for smoking measures using the alcohol consumption summary statistics. There were 10 loci showing colocalization between alcohol use disorder and smoking traits, including a functional analysis demonstrating pleiotropic effects between 2 genes and both smoking behaviors and gene expression. A second publication using MTAG with a smaller sample ($n = 5,692$ European ancestry; $n = 4,918$ African ancestry) examined 4 substance use traits among participants of European ancestry (opioid use disorder, cannabis use disorder, alcohol use disorder, and smoking initiation) and 3 substance use traits among participants of African ancestry (opioid use disorder, alcohol use disorder, and smoking trajectory).¹⁴ This study also had power to detect additional associations via the multi-trait approach. Of note, eight novel and significant genome-wide loci for smoking initiation were detected in the European ancestry sample and one novel locus for smoking trajectory was detected in the African ancestry sample. Additionally, 10 novel genome-wide significant loci were identified in relationship to alcohol use disorder in the European ancestry sample. Overall, only 5 of 19 novel loci identified in the analysis of the European sample were significantly associated with 2 or more substances.

Many studies have converged on the same genes and/or physiological pathways as shared components of underlying risk for tobacco and alcohol use across diverse populations. Such findings hold substantial promise for the development of new classes of treatments and personalized medicine. However, these genetic risk factors may differ among populations with less genetic similarity. One strategy to examine this has been the use of multiancestry transcriptome-wide association studies, whereby expression data are integrated with GWAS data to identify correlations between associated SNPs and patterns of gene expression.¹⁵⁸ This

approach was applied to tobacco use phenotypes to identify additional genes and perform *in silico* drug repurposing analysis that identified possible alternative treatments for nicotine dependence.¹⁵⁹ These results highlight the importance of recruitment of large samples from diverse populations across the world as further efforts are made to develop personalized medicine approaches for tobacco and alcohol use and co-use.

The Potential for Personalized Medicine for Prevention and Cessation

As researchers continue to identify genetic loci associated with tobacco and alcohol use, some specific genetic markers and their related biological markers have been studied in the context of treatment trials to assess whether individuals with specific variants show differential likelihood of successfully quitting. Most of these studies have been conducted for treatment for either tobacco or alcohol use, but a few have encompassed treatment for both substances. NCI Monograph 20, published in 2009, presented initial forays into pharmacogenetic studies for cessation of tobacco use, providing potential avenues to design personalized treatment for smoking cessation⁸ (personalized approaches to tobacco cessation are further discussed in chapter 7).

Surveys have shown that individuals want information about their personal genetic risk.¹⁶⁰ Providing genetic risk information accompanied by education/coaching about behavior change¹⁶¹ could potentially strengthen efforts to reduce tobacco and alcohol use. However, such approaches have yet to be applied to tobacco and alcohol co-use; as of 2026, the evidence is mixed that such information improves success of behavioral interventions for either tobacco or alcohol use.^{157,160-162}

Personalized Treatment for Tobacco Use

The field of pharmacogenomics seeks to understand how genetic variation influences the pharmacokinetic (absorption, distribution, metabolism, and excretion) and pharmacodynamic (interaction with receptors, transporters, and downstream targets) properties of a substance. These characteristics may affect treatment response and the potential for adverse events.¹⁶³ The nicotine metabolite ratio (NMR) measures the ratio of 3'-hydroxycotinine (3HC) to cotinine; higher ratios indicate faster nicotine clearance and lower levels of nicotine in the blood.¹⁶⁴ The NMR is a validated measure of nicotine metabolism that can be ascertained using saliva, plasma, or urine.¹⁶⁵

The NMR is as a proxy for variation in the *CYP2A6* gene, because the CYP2A6 protein is largely responsible for the metabolism of nicotine.^{166,167} Clinical studies typically separate participants into slow metabolizers (usually those in the first quartile of NMR) and fast metabolizers (all others, or those in the highest quartile of NMR) to determine whether different treatments (e.g., nicotine replacement therapy [NRT], bupropion, varenicline, placebo with counseling) are more or less effective in one group than the other. Some data support using NRT for slow metabolizers and non-nicotine treatments for normal metabolizers.^{165,168,169} Together these and other studies support the possibility that NMR could be a predictive biomarker contributing to improved selection of treatments for smoking cessation.¹⁶⁷

Studies have also examined *CYP* gene variants and *CYP* activity in people who smoke from different racial and/or ethnic groups. *CYP2A* activity levels differ across several groups but do not fully account for differences in smoking intensity and exposure to carcinogens.¹⁷⁰⁻¹⁷²

Further studies of race and/or ethnic variation in metabolism of carcinogens and nicotine are needed to help account for differences in lung cancer incidence between demographic groups that appear independent of smoking intensity.¹⁷³ *CYP2A6* is thought to be an important target for the optimization of smoking treatments,¹⁷⁴ but its potential has not yet been realized.¹⁷⁵

Variation in nAChR subunit genes has also been associated with differences in ability to quit smoking and may vary according to treatment.^{167,168,176-180} A 2022 systematic review included studies of individuals of European ancestry and evaluated multiple variants across the *CHRN* genes.¹⁸⁰ The review found that variants in the *CHRNA5-A3-B4* gene cluster are risk alleles for cessation failure.¹⁸⁰ Results of pharmacotherapy studies suggested that NRT and bupropion might support abstinence among people with the high-risk alleles. However, the review did not assess combined NRT and varenicline, and the odds ratios for cessation were not significant for any therapy tested.¹⁸⁰ As of 2026, data for other nicotinic receptor subunits genes are lacking. In summary, this research represents the first foray into precision treatment to promote smoking cessation.

Personalized Treatment for Alcohol Use Disorders

Lohoff compiled a comprehensive review in 2020¹⁶³ describing the status of pharmacogenomic studies of alcohol use disorder. This included an evaluation of U.S. Food and Drug Administration (FDA)-approved medications for alcohol use disorder (disulfiram, acamprosate, and naltrexone) along with medications used off-label for alcohol use disorder (topiramate, gabapentin, baclofen, ondansetron, varenicline). For each of the FDA-approved medications, specific genetic variants have been studied in clinical trials based on genes known or believed to be related to the primary target for the medication. Variants in the *DBH*, *OPRM1*, and *ALDH2* genes were examined in a few studies; in some cases, specific alleles were associated with improved treatment response with disulfiram compared to the alternate allele, but these were small studies that have not been replicated.¹⁶³

Naltrexone primarily targets the μ -opioid receptor, and a specific variant in *OPRM1* gene, rs1799971, corresponding to an amino acid substitution (asparagine to aspartate: Asn40Asp) has been widely studied in multiple clinical trials.¹⁶³ A meta-analysis evaluated seven randomized control trials (RCTs) that examined the effect of Asn40Asp on naltrexone treatment for heavy drinking or alcohol use disorder. This meta-analysis identified a moderating effect of Asn40Asp on drinks per day, but this effect was not significant when taking into account multiple comparisons; the authors concluded that the available evidence remains unclear about whether this genetic variant predicts naltrexone treatment response.¹⁸¹

Acamprosate is believed to target N-methyl-D-aspartic acid (NMDA) receptors and indirectly affect γ -aminobutyric acid type A (GABA_A) neurotransmission.¹⁸² Polymorphisms in *GATA4*, *DRD2*, *GABRA6*, *GABRB2*, and *GRIN2B* have been studied in relation to treatment with acamprosate, and overall evidence suggests that individuals who have an initial desire to remain abstinent and receive acamprosate treatment may have reduced risk of relapse to drinking.¹⁸³ The efficacy of treatment may be partially moderated by variation in these genes, but results are limited.¹⁸³

Topiramate increases GABA transmission, leading to inhibition of glutamate, and is used as an anticonvulsant medication; this medication requires close monitoring for side effects.¹⁸⁴ A meta-analysis of seven RCTs found topiramate to be significantly better than placebo at facilitating decreased drinking, but the effect was moderate.¹⁸⁵ Furthermore, emerging evidence suggests that individuals with the C-allele of rs2832407 in the *GRIK1* gene may respond better to topiramate treatment.¹⁸⁴

For the other medications, few or no pharmacogenomic studies have been conducted. As with treatment for tobacco use, additional studies are needed before large-scale clinical efforts to implement personalized treatments for alcohol use disorder should be undertaken. For example, research is just beginning on the potential of somatostatin (SST), vasoactive intestinal peptide (VIP), glucagon-like peptide-1 (GLP-1), nociceptin (NOP), and neuropeptide S (NPS) as targets for alcohol use disorder pharmacotherapies.¹⁸⁶ Interest has also emerged in treating alcohol use disorder with psychedelic drugs based on some promising results,¹⁸⁷⁻¹⁸⁹ but data to consider personalized approaches are lacking.

Personalized Treatment for Comorbid Tobacco and Alcohol Use Disorders

Varenicline, a pharmacotherapy for smoking cessation, is a partial agonist at the $\alpha 4\beta 2$ nAChRs, but a full agonist at $\alpha 7$ nAChRs, and likely affects other nAChR subtypes.¹⁹⁰⁻¹⁹² Several studies have also examined use of varenicline for alcohol use disorder.¹⁶³ Two trials of varenicline for alcohol use disorder suggested varenicline could be effective in reducing heavy drinking days or alcohol consumption in people who smoke at least 10 cigarettes per week¹⁹³ and in both people who do and do not smoke.¹⁹⁴ Evidence also indicates that varenicline can facilitate smoking cessation among people who drink heavily and also smoke.¹⁹⁵ However, while varenicline use for alcohol use disorder has shown some positive effects,¹⁹⁶ it is not FDA approved for this indication (see chapter 7). Most recently, a 2023 meta-analysis of 22 RCTs of varenicline for treatment of alcohol use disorder reports reduction in some but not all measures of alcohol use and use behavior.¹⁹⁷

No studies were identified that examined genetic factors (e.g., variation in the *CHRN* genes) that may moderate treatment responses to varenicline use for co-use of tobacco and alcohol. Previous studies focused on either tobacco or alcohol use may have collected data from participants that used both substances; however, these studies are likely to be underpowered to draw meaningful conclusions about the complex genetic interactions relating to co-use behaviors.

In sum, there is evidence that varenicline may be a useful treatment option for people who both smoke and have alcohol use disorder. However, effect sizes are modest and understanding of variation in effectiveness is limited. As more well-powered clinical studies examining various therapies for cessation of tobacco and alcohol are conducted, opportunities for treating co-use and for exploring personalized treatment approaches will likely increase. See chapter 7 for further discussion of pharmacotherapies for tobacco and alcohol use.

Box 6.1. The Potential Role of Glucagon-Like Peptide-1 Agonists in Treating Substance Use Disorders

GLP-1 receptor agonists were originally developed as treatments for type 2 diabetes and are now commonly used to treat obesity.¹⁹⁸ These medications mimic the incretin hormones that stimulate the release of insulin in response to eating; they suppress appetite and decrease body weight by activating gut-brain signaling mechanisms involving several brain regions.¹⁹⁹ FDA approval of GLP-1 medications to treat type 2 diabetes and obesity has resulted in their wide use, and patients have anecdotally reported unanticipated decreases in their use of alcohol and other addictive substances.²⁰⁰ In addition, studies conducted in animals support a potential role for these medications in treating alcohol use disorder.^{201,202} These findings have resulted in a small but growing number of trials examining the effects of these medications on substance use. Martinelli and colleagues (2024)²⁰³ identified 5 RCTs examining tobacco ($n = 2$), alcohol ($n = 2$), and cocaine use ($n = 1$) in a total of 630 participants receiving either of 2 GLP-1 agonists (exenatide or dulaglutide). Of these five studies, one observed increased abstinence from smoking in the medication group and one observed reduced alcohol consumption in the medication group (compared with patients receiving placebo). Additionally, a study comparing patients taking semaglutide for type 2 diabetes to patients taking other antidiabetes medications, found that those taking semaglutide had a lower risk of utilizing health care for tobacco use disorder, suggesting that the medication may have reduced their tobacco use.²⁰⁴ Other studies have found that semaglutide taken once per week reduced craving and some measures of consumption in people with alcohol use disorder,²⁰⁵ and once weekly exenatide increases tobacco cessation success and weight loss.²⁰⁶ Interestingly, a further study of exenatide for smoking cessation reported that it was only associated with cessation for a specific genotype (*CHRNA5* rs16969968 GG),²⁰⁷ a gene known to be associated with response to treatment for smoking cessation.¹⁷⁷ Additional RCTs are needed to clarify the potential role of GLP-1 agonists in treating substance use disorders, although their widespread use will also result in substantial data from observational studies.

Using Large-Scale Genetic Studies to Predict Cessation

As the field of genetics has moved from candidate gene studies to large-scale GWAS, there has also been a movement from studies of single genes predicting cessation to using information from many genes to predict successful cessation. A goal of this approach is to use results of large-scale GWAS to generate polygenic scores accounting for clinically significant variation in cessation success and other aspects of tobacco and alcohol use. Polygenic scores are an estimate of genetic risk based on variation in SNPs calculated with results from GWAS and other data.²⁰⁸

Most polygenic scores have been derived in populations of European ancestry and therefore have greater predictive accuracy among genetically similar populations.²⁰⁹ Research is underway to improve the predictive ability of polygenic scores across different populations.²¹⁰ For example, Lennon and colleagues (2024)²¹¹ have proposed a detailed polygenic scores pipeline designed to improve the development and validation of polygenic scores and prevent exacerbation of health disparities associated with polygenic scores derived primarily from European ancestry populations.

The use of polygenic scores represents the next frontier in translating knowledge of genetic risk into improved health.¹⁶⁰ However, research is needed to determine whether this approach can contribute to addressing tobacco and alcohol use. Utility of polygenic scores for public health goals depends on both the capacity to identify subjects differing in risk and the availability of specific interventions that could help people with different polygenic scores for initiation, continued use, and cessation. A 2022 study to identify polygenic scores for alcohol use disorder and alcohol use disorder severity found that the odds ratio for developing alcohol use disorder associated with the highest decile of the polygenic score (OR = 1.96, 95% CI = 1.54–2.51) was similar to those for having a first-degree family history²¹² and that both family history and polygenic score provided unique information about risk. Whether this kind of risk information can be used to improve cessation of tobacco and/or alcohol use is not yet established.

Chapter Summary

Understanding how genetic variation influences the risk of substance use, including the use of tobacco and alcohol, can contribute to the prevention and treatment of substance use disorders. Genetic studies have focused on identifying variants related to nicotine, the primary addictive component of tobacco products, and ethanol, the primary addictive component of alcohol products. Complex behaviors, such as tobacco use, alcohol use, and tobacco-alcohol co-use, develop in stages over time, as a result of the interaction of thousands of genetic factors with diverse environmental factors. As of 2026, most genetic research on substance use has been conducted in adults. However, new longitudinal studies—the Adolescent Brain Cognitive Development (ABCD) study and the Healthy Brain and Child Development (HBCD) study—are underway to help understand the onset of substance use in adolescents and younger children. The topic of genetic contributions to tobacco use was reviewed in NCI Monograph 20, *Phenotypes and Endophenotypes: Foundations for Genetic Studies of Nicotine Use and Dependence*, published in 2009. Since that report's publication, advances in technology—most notably the development of high-throughput genotyping technologies enabling genome-wide association studies (GWAS)—have contributed to significant advances in the field.

Research into how the brain responds to nicotine and ethanol and to the use of tobacco products and different types of alcohol-containing beverages reveals a complex interplay of many brain regions that contribute to altered neurobehavioral processes involved in substance use and development of substance use disorders. The triadic neurobehavioral model describes the neurophysiological mechanisms underlying substance use disorders in terms of three functional domains (incentive salience, negative emotional states, and executive function) mediated by

distinct neurobiological circuits (basal ganglia, extended amygdala, and prefrontal cortex, respectively). All addictive substances, including nicotine and ethanol, affect these three major neurobiological circuits; additionally, substance-specific neurobiological effects have also been identified.

Addictive behaviors, including tobacco and alcohol use, involve changes in the production, release, and binding of dopamine in the brain. Over time, tolerance (when a greater amount of the substance is needed to elicit the same response) develops. Cross-tolerance (when repeated administration of one substance induces a decreased response to another substance) is associated with co-use of tobacco and alcohol and has important implications for prevention and treatment interventions.

General processes of addiction influence response to multiple substances with co-use leading to additive effects on reward systems and development of substance use disorders. This conclusion is supported by neurophysiological findings from both human and rodent studies. These shared processes at the genetic and neurophysiological levels help explain why co-use of tobacco and alcohol is especially common in people who use tobacco and who drink on average at higher levels, such as more than one drink a day for women and two drinks per day for men.

Neuroimaging studies support the importance of the classic triadic neurobehavioral model of addiction—but also extend it. Altered salience attribution, negative emotional states, and dysregulated prefrontal function are at the core of substance use disorders. However, higher order processes, such as changed appraisal of subjective value, altered self-directed processing, and changes in flexible learning and memory in individuals with substance use disorders also play a critical role in substance use and substance use disorders. The brain networks identified from the human neuroimaging studies of tobacco and alcohol use differ slightly from those identified in animal (rat, mouse) models; this is likely attributed to differences in experimental procedures and imaging tools, as well as interspecies differences.

Studies of people who use tobacco and alcohol as well as other addictive substances suggest there may be several different neurophysiological precursors that can lead to substance use and/or substance use disorders. Ongoing longitudinal studies that include sophisticated brain imaging and extensive phenotyping concerning psychological traits should help further elucidate these potential precursor phenotypes and may help inform the development of pharmacotherapies to prevent the onset of tobacco and alcohol use and co-use.

Genetic studies further illuminate the relationship between genes and substance use. Studies of monozygotic (identical) and dizygotic (fraternal) twins have been used to estimate heritability, a statistical concept that estimates how well differences in genetic factors within a population account for differences in a particular trait. Heritability ranges from zero to one, with values close to zero indicating that the trait is mostly due to environmental factors, and higher values indicating the trait is largely due to genetic factors. Heritability is specific to the population studied and can change as the environment or genetic makeup of a population changes. Geneticists use heritability to ascertain that a trait is determined, at least in part, by genetic factors, and to determine how much shared genetic variance exists between traits. Extensive

research has now demonstrated that, across populations, the risk for smoking and alcohol use is split roughly equally between genetic and environmental factors. Research suggests that environmental factors (e.g., substance use by peers and family, price, advertising) play a larger role in initiation of tobacco and alcohol use than genetic factors. Conversely, evidence suggests that genetic factors play a larger role in continued and increased substance use than environmental factors.

Prior to the availability of GWAS, genetic studies employed family-based linkage analyses or case-control association studies. While important, these studies had very limited ability to identify genes underlying behavioral traits, such as substance use, which result from the interaction of thousands of genetic factors, combined with environmental influences. Although GWAS represent an enormous advance, these studies also have limitations, which may include limited phenotypic assessment, difficulty controlling for population stratification, and limited ancestry diversity of study participants. Additionally, initial studies have focused either on tobacco use or alcohol use phenotypes, and few have examined tobacco–alcohol co-use. Progress is being made, however, thanks to the use of electronic medical records, the emergence of large “biobanks,” measures to promote data sharing, and other factors.

Large-scale human genetic research has identified numerous potential risk loci linked to both tobacco and alcohol use, whether individually or as co-occurring disorders. Of note, studies show that the genetic pathways that contribute to risk for tobacco and alcohol use disorders are similar across diverse populations. While many risk loci have not been mapped directly to specific genes, those that have confirm the significance of previously identified neurophysiological pathways (e.g., involving nicotinic acetylcholine receptors, *CHRN* genes). Additionally, variations in genes and proteins that affect the metabolism of nicotine (e.g., cytochrome P450, *CYP* genes) and ethanol (e.g., alcohol dehydrogenase, *ADH* genes; aldehyde dehydrogenase, *ALDH2* genes) have consistently been associated with individual responses to these substances, influencing the risk of increased use, and suggesting avenues for the development of pharmacotherapies or more effective use of existing therapies. In cases where GWAS results identify single nucleotide polymorphisms (SNPs) outside protein-coding regions of genes, the function of these is more difficult to predict; however, these SNPs could contribute to regulation of gene expression or be associated with a different, causally related SNP. Despite these advancements, developing effective treatments for substance use, including tobacco and alcohol co-use, tailored to individual genetic profiles is not yet a reality. The field of personalized medicine for substance use is still in its early stages, requiring further research to determine whether personalized strategies for tobacco cessation and alcohol cessation/reduction can be developed. Progress hinges on collaborative efforts among experts in physiology, pharmacology, genetics, and psychology, who must address the intricate interactions between genetic factors and environmental influences on tobacco and alcohol use.

In summary, significant strides have been made in understanding the brain’s response to nicotine and ethanol and identifying genetic factors linked to substance use. However, translating these findings into precise, effective treatments remains a challenge. Continued interdisciplinary research and integration of genetic and environmental data are crucial for advancing personalized medicine in the realm of substance use disorders.

Research Needs

Although the field has been successful at identifying genetic variants associated with nicotine and ethanol use, very few studies have carefully considered these behaviors together. Improved understanding of genetic associations and pathways that overlap between tobacco and alcohol use behaviors will provide important insight in the context of personalized medicine. Additional well-powered studies that combine brain imaging with genetics in children and adolescents, such as the HBCD study and ABCD study, have the potential to differentiate between functional brain differences that are predisposing to substance use and those that result from substance exposure. Such studies could also be strengthened by the further characterization of phenotypes and especially endophenotypes of tobacco and alcohol co-use at specific periods of initiation and use over the life course.

Further, more research is needed to develop prevention and treatment approaches that specifically address heterogeneity in the three neurofunctional domains related to addiction. Longitudinal studies of brain development and neurobehavioral characteristics are needed to better understand how these trait-like factors are involved in addiction and substance use across the lifespan. Ongoing cohort studies, such as the HBCD and the ABCD studies, should help address these questions through a combination of extensive phenotyping, brain imaging, and biospecimen collection.

Genetic and epidemiological analyses depend on consistent and meaningful definitions of use categories. For cigarettes, a threshold of having smoked at least 100 cigarettes is widely used to classify a person as having ever been an established user (e.g., rather than having tried smoking a few times). However, there is no standard for a minimum level of e-cigarettes or alcohol exposure for classifying participants as ever users. Establishing such thresholds and consideration of combined thresholds across both tobacco and alcohol products may facilitate research in this area. In addition, consistent measurement of various consumption patterns in longitudinal epidemiologic studies, such as nondaily smoking and drinking over the life course and analysis with genetic data, would further discovery of gene-environment interactions for tobacco and alcohol co-use.

Further analysis of the ontogeny of tobacco and alcohol co-use in diverse populations is needed. Such studies should continue efforts to address populations of diverse ancestry and to examine interactions between environment and the range of genetic and development variation over the entire life course. In addition, the neuroimaging literature suggests that there are sex differences in the neurobiological mechanisms underlying substance use disorders⁸³; research is needed to explore these differences.

Although *post hoc* strategies used to characterize the genes and variants emerging from GWAS have begun to identify pathways, few of the GWAS results have been pursued at the functional level. Most GWAS results do not fall within a gene with obvious function, so methods to quickly predict and test functional implications of individual variants must be expanded. One such method (Functional Mapping and Annotation of Genome-Wide Association Studies; FUMA) has been developed and is now widely used.^{213,214}

Although the field widely recognizes that gene-gene interactions and gene-environment interactions contribute to tobacco and alcohol use, studies have been underpowered to detect such interactions. This area of research is poised for the development of new methods, which should also consider environmental factors that change over time, such as the tobacco product marketplace. For example, the entry of e-cigarettes into the marketplace has resulted in high levels of adolescent use of e-cigarettes. These genetic characteristics and behavioral phenotypes could also be studied in relation to additional disease outcomes related to tobacco and alcohol co-use.

There remain many research questions related to the genetics of tobacco and alcohol use phenotypes and their diverse health effects. For example, the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) data were used to estimate the genetic correlation between smoking measures and lung cancer; in general, heavier smoking and lower smoking cessation were positively associated with increased risk for lung cancer and chronic obstructive pulmonary disease.²¹⁵ Further, variation in the *CHRNA5* gene, which is one of the loci most strongly associated with heavy smoking and failed smoking cessation,¹⁶⁷ is also one of the strongest associations with the development of lung cancer (see chapter 5).²¹⁵ It is also clear that there are genetic associations specific to the development of lung cancer that are not smoking related.²¹⁶ However, genetic variants of the locus coding the nicotine metabolizing genes (*CYP2A6*) displayed an inverse relationship with smoking behaviors; despite being associated with an increased risk of heavier smoking, lung cancer, and chronic obstructive pulmonary disease, they were also associated with successful smoking cessation.²¹⁵ This inverse relationship highlights the need to better understand how nicotine metabolism alters the risk of heavier smoking measured by cigarettes smoked per day, lung cancer, and chronic obstructive pulmonary disease while also contributing to increased smoking cessation. Disentangling the common and specific genetic contributions to smoking and lung cancer may be useful in developing new treatments or treatment approaches. Together these results highlight the importance of investigating the genetic associations between behavior and risk to determine whether they can inform the development of improved approaches to cessation.

Similarly, there is a relationship between the genetics of alcohol consumption and aerodigestive tract cancers. Multiple risk variants in the *ADH* and *ALDH* genes have emerged from GWAS for aerodigestive tract cancers (see chapter 5).²¹⁷ There is evidence that tobacco and alcohol use leads to genetic variations in tumor suppressor genes, along with other disruptions to cell-cycle processes, which contribute to the development of oral cancers.²¹⁸ Emdin and colleagues (2021)²¹⁹ report that a polygenic score derived from 12 independent genetic variants for cirrhosis of the liver identifies individuals who are most susceptible to the hepatotoxic effects of excess alcohol consumption or obesity. Strong genetic predictors of excess risk related to behavior and obesity could potentially guide more targeted interventions. Overall, it is a significant research gap that few genetic studies as of 2026 have directly addressed phenotypes of co-use of tobacco and alcohol.

Further research is needed to optimize health communications related to family history, and to genetic and environmental influences of risk of tobacco and alcohol use, and co-use. Notably, it is unclear from the present literature whether information about family history improves responses to health communications or influences decision-making in a positive way. Further research is also needed on how stigma influences health cognitions related to individual and family history.

Conclusions

1. **Tobacco and alcohol use affect multiple complex neurophysiological processes in the brain.** Networks of brain regions that include the nucleus accumbens; amygdala; habenula; interpeduncular nucleus; hippocampus; insula; as well as cingulate, orbitofrontal, and prefrontal cortices influence how people respond to nicotine and ethanol, the primary substances in tobacco and alcohol products that lead to dependence and addiction.
2. **Large-scale human genetic studies have identified thousands of genetic variants associated with tobacco and alcohol use.** Variation in genes and in proteins involved in the metabolism of nicotine and ethanol have been associated with an individual's response to these substances, patterns of continued use, and risk for sustained use and dependence. These associations provide a mechanistic basis for some of the observed differences in substance use at the population level.
3. **Multiple risk loci have been mapped to genes known to be involved in nicotine and ethanol use and their physiological effects.** The pathways of interest include dopaminergic, GABAergic, glutamatergic, and stress response pathways. These pathways influence how genetic variations affect individual responses to nicotine and ethanol, patterns of continued use, and the potential development of substance use disorders related to other drugs.
4. **Genetic studies have identified a substantial number of genetic variants that are associated with both alcohol use and tobacco use across populations, providing evidence for shared underlying mechanisms.** A better understanding of the shared biological mechanisms from additional genetic studies will inform efforts to prevent use disorders and develop pharmacotherapies for tobacco and alcohol co-use and polyuse with other substances.
5. **Research to understand neurophysiologic and genetic factors contributing to tobacco and alcohol use and their co-use is beginning to inform precision medicine treatment approaches.** An understanding of the complex interplay between genetic and environmental factors is essential for personalized treatments for tobacco and alcohol use to be most effective. Additional research is needed to effectively use existing therapies and develop personalized pharmacotherapies for tobacco and alcohol co-use.

Appendix 6A Selected Genome-Wide Association Studies of Tobacco and Alcohol Published Since 2018

Study	Phenotype(s)	Sample ^a	Selected results
23andMe Research Team 2019 ²²⁰	Alcohol Smoking	UK Biobank and 23andMe ($N = 939,908$) Replication 10 cohorts from 7 studies ($n = 35,445$)	46 of 99 general risk tolerance loci contain lead SNP for at least 1 other GWAS - Genes near SNPs are highly expressed in the brain
Deak et al. 2022 ²²¹	Alcohol	Million Veteran Program ($n = 218,623$ European American and $n = 29,132$ African American)	15 genome-wide significant loci for “maximum habitual alcohol intake” “Maximum habitual alcohol intake” is genetically correlated with measures of alcohol-related problems, but alcohol consumption measures load on a separate factor
Deak et al. 2022 ²²²	Alcohol Cannabis Tobacco Opioid	7 cohorts: Million Veteran Program, Psychiatric Genomics Consortium, iPSYCH, FinnGen, Partners Biobank, Vanderbilt University Medical Center (BioVU), Yale-Penn 3 $N = 639,063$ ($n = 84,877$ African ancestry; $n = 544,186$ European ancestry)	18 independent, genome-wide, significant loci for opioid use disorder, including <i>OPRM1</i> - Strong genetic correlations of opioid use disorder with alcohol use disorder ($r_g = 0.77$) and cannabis use disorder ($r_g = 0.82$)
Kember et al. 2023 ¹³⁰	Alcohol	Million Veteran Program longitudinal data ($N = 409,630$; $n = 296,989$ European American; $n = 80,764$ African American; $n = 31,877$ Hispanic American) - Validation in Vanderbilt University Medical Center (BioVU) ($n = 66,903$ European American; $n = 12,384$ African American) - UK Biobank ($n = 123,561$ European ancestry; $n = 1,182$ African ancestry)	26 loci associated with alcohol use disorder and 22 loci associated with AUDIT-C (some ancestry-specific and some novel) - Excluding subjects reporting abstinence, additional loci were found (7 for alcohol use disorder and 8 for AUDIT-C) - Mediation analysis revealed set of variants with effects on alcohol use disorder that are not mediated through alcohol consumption
Kranzler et al. 2019 ²²³	Alcohol	- Million Veteran Program ($N = 274,424$) - Replication samples: Penn Medicine BioBank ($n = 9,965$), Yale-Penn study ($n = 9,739$)	18 genome-wide significant loci 5 associated with AUDIT-C and alcohol use disorder 8 associated with AUDIT-C only 5 associated with alcohol use disorder only - Polygenic scores for both traits replicated in 2 independent samples
Liu et al. 2019 ¹	Alcohol Smoking	GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN): N of up to 1.2 million (depending on phenotype)	- Total of 566 variants in 406 loci associated with tobacco use and/or alcohol use 150 loci showed evidence for pleiotropic association

Appendix 6A (continued)

Study	Phenotype(s)	Sample ^a	Selected results
Mallard et al. 2022 ²²⁴	Alcohol Smoking Psychiatric disorders	Discovery: - UK Biobank ($n = 147,267$); Netherlands Twin Register ($n = 9,975$); Avon Longitudinal Study of Parents and Children ($n = 3,582$) Replication: - UK Biobank different subset ($n = 239,719$); Collaborative Study on the Genetics of Alcoholism (COGA, $n = 6,390$); Vanderbilt University Medical Center (BioVU, $n = 91,602$)	- Identification of a 2-factor structure at the genetic level exemplified by “consumption” and “problems” which are: - Highly correlated ($r_g = 0.80$) - Strongly associated with alcohol dependence ($r_g = 0.67$) - Moderately associated with other psychiatric disorders, including cigarettes per day
Miller & Gizer 2024 ²²⁵	Alcohol Imaging	23andMe, GSCAN, UK Biobank, Million Veteran Program, AlcGen, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), Psychiatric Genomics Consortium, FinnGenR6, Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Various combinations depending on phenotype sample sizes: - Sensation seeking: 710,971 - Alcohol consumption: 1,388,120 - Alcohol use disorder: 220,182 - Neuroimaging: ~30,000	- Sensation seeking, alcohol consumption, alcohol use disorder, and neuroimaging - Support for shared genetic architecture between sensation seeking and alcohol consumption, via genes expression in midbrain and striatal tissues, and genetic variants associated with increased cortical surface area - Alcohol consumption and alcohol use disorder show overlap with genetic variants associated with decreased frontocortical thickness - Mediation models provide evidence of alcohol consumption mediating associations between sensation seeking and alcohol use disorder
Rabinowitz et al. 2022 ²²⁶	Alcohol Cannabis Tobacco Common substance use factor Imaging	71 neuroimaging studies from the ENIGMA Consortium ($N = \sim 33,000$) - GWAS summary statistics for tobacco and alcohol use from 23andMe and GSCAN cohorts ($N = \sim 1.2$ million) - GWAS summary statistics for cannabis use from International Cannabis Consortium, UK Biobank, and 23andMe ($N = 184,765$) - Adolescent Brain Cognitive Development (ABCD) study ($N = 10,403$)	8 significant negative correlations - Alcohol drinks per week and average cortical thickness - Intracranial volume with age of smoking initiation 5 positive genetic correlations - Insula surface area and lifetime cannabis use - Common substance use behavior genetic factor and pericalcarine surface area - There is a shared genetic etiology between cortical brain morphology and substance use behaviors

Appendix 6A (continued)

Study	Phenotype(s)	Sample ^a	Selected results
Risner et al. 2021 ²²⁷	Alcohol Smoking Psychiatric disorders	Pooled Database of Genotypes and Phenotypes (dbGAP) samples ($n = 6,394$, European ancestry); National Longitudinal Study of Adolescent to Adult Health (Add Health) Wave IV ($n = 3,061$, European ancestry)	- Nicotine dependence (cigarettes per day, AUDIT-C, AUDIT-P, neuroticism, schizophrenia, depression, BMI, self-perceived risk-taking, educational attainment) - Partial correlations between nicotine dependence and polygenic scores developed for each of the individual nine phenotypes - Multi-trait polygenic score also shows similar estimates with nicotine dependence, but depends on phenotype
Toikumo et al. 2024 ¹³	Tobacco	PsychMerge network biobanks: Vanderbilt University Medical Center (BioVU), Mass General Brigham Biobank, Penn Medicine BioBank, Million Veteran Program, UK Biobank $N = 898,680$ subjects ($n = 495,005$ European American, $n = 114,420$ African American, $n = 44,365$ Latin American ancestry, and $n = 244,890$ European ancestry from UK Biobank)	- Tobacco use disorder based on electronic health records 88 independent risk loci 461 potential risk genes, primarily expressed in the brain - Tobacco use disorder genetically correlated with many other health outcomes
Wang et al. 2023 ²²⁸	Alcohol	Michigan Longitudinal Study ($n = 665$; European ancestry)	- Problem alcohol use that combines frequency of alcohol use, maximum drinks in 24-hour period, and alcohol use problems at 4 assessments during young adulthood (11–29 years) - Problem alcohol use polygenic score was significantly associated with alcohol-related problems in young adulthood even after adjusting for: - Demographic covariates - Parental alcohol use disorder - Drinking and alcohol use problems in early and mid/late adolescence
Xu et al. 2020 ²²⁹	Smoking	Million Veteran Program (MVP; $n = 286,118$), includes $n = 209,915$ European American, $n = 54,867$ African American, $n = 21,336$ Hispanic American) Meta-analysis with GSCAN ($n = 842,717$)	- EMR-based smoking trajectories - In MVP: 18 loci for smoking trajectory in European Americans; 1 locus in African Americans; 1 locus in Hispanic Americans - In MVP and GSCAN: 99 loci for smoking initiation - In MVP and GSCAN: 13 loci for smoking cessation
Zhang et al. 2022 ²³⁰	Alcohol Nicotine Cannabis Opioid	National Epidemiologic Survey on Alcohol and Related Conditions-III ($n = 22,848$ subjects, $n = 12,505$ predominately European ancestry)	21 independent SNPs and 17 gene-based loci for substance use disorders - Some SNPs/loci are substance-specific, some are shared

Appendix 6A (continued)

Study	Phenotype(s)	Sample ^a	Selected results
Zhou et al. 2020 ²³¹	Alcohol	<i>N</i> = 435,563 European ancestry subjects from Million Veteran Program Phase 1 (<i>n</i> = 202,004), MVP Phase 2 (<i>n</i> = 65,387), Psychiatric Genomics Consortium (<i>n</i> = 46,568), and UK Biobank (<i>n</i> = 121,604) Replication of polygenic score in Vanderbilt University Medical Center (BioVU) (<i>n</i> = 67,589)	• 29 independent risk variants (19 novel) • Problem alcohol use was genetically correlated with 138 phenotypes • Heritability analyses of problem alcohol use showed enrichments in the brain and in conserved and regulatory genomic regions
Zhou et al. 2022 ²³²	Alcohol Tobacco	5 cohorts (<i>N</i> = 13,551): • Thai study of genetics methamphetamine dependence – Global Screening Array (<i>n</i> = 532) • Thai study of genetics of methamphetamine dependence – Multi-Ethnic Global Array (<i>n</i> = 2,370) • Million Veteran Program-East Asian Americans (<i>n</i> = 6,955) • Han Chinese – Global Screening Array (<i>n</i> = 3,381) • Han Chinese – Cyto12 array (<i>n</i> = 313) • Independent evaluation of polygenic score in Genetic Epidemiology Research in Adult Health and Aging (<i>n</i> = 4,464 East Asians)	• Detected 2 well-known loci, one in <i>ADH1B</i> and one in <i>BRAP</i> near <i>ALDH2</i> • Alcohol use disorder polygenic score associated with days per week of alcohol consumption and nominally associated with pack-years of smoking and ever versus never smoking
Zhou et al. 2023 ²³³	Alcohol	Multiple cohorts (<i>N</i> = 1,079,947; <i>n</i> = 903,147 European ancestry; <i>n</i> = 122,571 African ancestry; <i>n</i> = 38,962 Latin American ancestry; <i>n</i> = 13,551 East Asian ancestry; <i>n</i> = 1,716 South Asian ancestry), including Million Veteran Program, UK Biobank, FinnGen, iPSYCH, QIMR Berghofer Medical Research Institute, Psychiatric Genomics Consortium, Yale-Penn 3, East Asian cohorts	• Problematic alcohol use based on DSM-IV alcohol dependence and AUDIT-P scale • 110 independent risk variants • High degree of cross-ancestral similarity in genetic architecture of problematic alcohol use • Fine mapping across ancestries allowed narrowing of putative functional variants • Transcriptome-wide association study and chromatin interaction analyses implicated brain-expressed genes • Polygenic score derived from multiple ancestries improves predictability and explains more variance relative to single-ancestry polygenic score

Note. ABCD = Adolescent Brain Cognitive Development; AUDIT-C/AUDIT-P = Alcohol Use Disorders Identification Test (C = Concise; P = Problem); BMI = body mass index; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (Fourth Ed.); EMR = electronic medical record; GSCAN = GWAS and Sequencing Consortium of Alcohol and Nicotine use; GSCAN2 = GWAS and Sequencing Consortium of Alcohol and Nicotine use 2; GWAS = genome-wide association study; *N* = full study sample; *n* = subpopulation sample; MTAG = multi-trait analysis of GWAS; SNP = single nucleotide polymorphism. Four key GWAS of tobacco and alcohol^{2,4,11,14} are presented in Table 6.1

^aPopulation descriptors (e.g., European American, European ancestry) are quoted from the cited studies.

Appendix 6B Literature Search Strategy

To identify relevant studies, the following search strings were used in PubMed: “GWAS and nicotine”; “genetics and smoking”; “smoking and imaging studies”. Searches were conducted between June and December 2023 to identify peer-reviewed studies published since PubMed inception through December 2023. Studies were also identified based on reviewing reference lists and review articles cited in key papers and/or presentations at scientific meetings, such as the NIDA Genetics and Epigenetics Cross-Cutting Research Team Meeting. Additional studies published after 2023 were incorporated into the chapter based on their relevance.

References

1. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet.* 2019;51(2):237-244. doi:10.1038/s41588-018-0307-5.
2. Saunders G, Wang X, Chen F, et al. Genetic diversity fuels gene discovery for tobacco and alcohol use. *Nature.* 2022;612(7941):720-724. doi:10.1038/s41586-022-05477-4.
3. Hartz SM, Bierut LJ. Genetics of addictions. *Clin Lab Med.* 2010;30(4):847-864. doi:10.1016/j.cll.2010.07.005.
4. Hatoum AS, Colbert SMC, Johnson EC, et al. Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. *Nat Mental Health.* 2023;1(3):210-223. doi:10.1038/s44220-023-00034-y.
5. Quach BC, Bray MJ, Gaddis NC, et al. Expanding the genetic architecture of nicotine dependence and its shared genetics with multiple traits. *Nat Commun.* 2020;11(1):5562. doi:10.1038/s41467-020-19265-z.
6. Schlaepfer I, Hoft N, Ehringer M. The Genetic components of alcohol and nicotine co-addiction: from genes to behavior. *CDAR.* 2008;1(2):124-134. doi:10.2174/1874473710801020124.
7. Tielbeek JJ, Vink JM, Polderman TJC, Popma A, Posthuma D, Verweij KJH. Genetic correlation of antisocial behaviour with alcohol, nicotine, and cannabis use. *Drug Alcohol Depend.* 2018;187:296-299. doi:10.1016/j.drugalcdep.2018.03.020.
8. National Cancer Institute. *Phenotypes and Endophenotypes: Foundations for Genetic Studies of Nicotine Use and Dependence.* Tobacco Control Monograph No. 20. NIH Publication No. 09-6366. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2009.
9. Tabor HK, Risch NJ, Myers RM. Candidate-gene approaches for studying complex genetic traits: practical considerations. *Nat Rev Genet.* 2002;3(5):391-397. doi:10.1038/nrg796.
10. U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
11. Cheng Y, Dao C, Zhou H, et al. Multi-trait genome-wide association analyses leveraging alcohol use disorder findings identify novel loci for smoking behaviors in the Million Veteran Program. *Transl Psychiatry.* 2023;13(1):148. doi:10.1038/s41398-023-02409-2.
12. Kember RL, Vickers-Smith R, Xu H, et al. Cross-ancestry meta-analysis of opioid use disorder uncovers novel loci with predominant effects in brain regions associated with addiction. *Nat Neurosci.* 2022;25(10):1279-1287. doi:10.1038/s41593-022-01160-z.
13. Toikumo S, Jennings MV, Pham BK, et al. Multi-ancestry meta-analysis of tobacco use disorder identifies 461 potential risk genes and reveals associations with multiple health outcomes. *Nat Hum Behav.* 2024;8(6):1177-1193. doi:10.1038/s41562-024-01851-6.
14. Xu H, Toikumo S, Crist RC, et al. Identifying genetic loci and phenomic associations of substance use traits: A multi-trait analysis of GWAS (MTAG) study. *Addiction.* 2023;add.16229. doi:10.1111/add.16229.
15. Witte JS. Genome-wide association studies and beyond. *Annu Rev Public Health.* 2010;31:9-20. doi:10.1146/annurev.publhealth.012809.103723.
16. Tam V, Patel N, Turcotte M, Bossé Y, Paré G, Meyre D. Benefits and limitations of genome-wide association studies. *Nat Rev Genet.* 2019;20(8):467-484. doi:10.1038/s41576-019-0127-1.
17. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Alcohol Consumption and Ethyl Carbamate.* Lyon (FR): International Agency for Research on Cancer; 2010. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 96.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK326568>.
18. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Personal Habits and Indoor Combustions.* Lyon (FR): International Agency for Research on Cancer; 2012. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100E.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK304391>.
19. U.S. Department of Health and Human Services. *Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.

20. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. Printed with corrections, January 2014.
21. Volkow ND, Blanco C. Substance use disorders: a comprehensive update of classification, epidemiology, neurobiology, clinical aspects, treatment and prevention. *World Psychiatry*. 2023;22(2):203-229. doi:10.1002/wps.21073.
22. Salvatore JE, Gottesman, II, Dick DM. Endophenotypes for alcohol use disorder: an update on the field. *Curr Addict Rep*. 2015;2(1):76-90. doi:10.1007/s40429-015-0046-y.
23. Cho J, Stone MD, Leventhal AM. Anhedonia as a phenotypic marker of familial transmission of polysubstance use trajectories across midadolescence. *Psychol Addict Behav*. 2019;33(1):15-25. doi:10.1037/adb0000427.
24. Dowling GJ, Hoffman EA, Cole KM, Wargo EM, Volkow N. The ABCD and HBCD studies: longitudinal studies to inform prevention science. *Focus (Am Psychiatr Publ)*. 2024;22(4):449-457. doi:10.1176/appi.focus.20240016.
25. Volkow ND, Koob GF, Croyle RT, et al. The conception of the ABCD study: from substance use to a broad NIH collaboration. *Dev Cogn Neurosci*. 2018;32:4-7. doi:10.1016/j.dcn.2017.10.002.
26. Bierut Laura J. Genetic vulnerability and susceptibility to substance dependence. *Neuron*. 2011;69(4):618-627. doi:10.1016/j.neuron.2011.02.015.
27. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary guidelines for Americans, 2020-2025. 9th Edition. 2020 [cited 2026 Mar 27]. Available from: https://www.dietaryguidelines.gov/sites/default/files/2021-03/Dietary_Guidelines_for_Americans-2020-2025.pdf.
28. World Cancer Research Fund/American Institute for Cancer Research. Alcoholic drinks and the risk of cancer. Continuous Update Project Expert Report. 2018 [cited 2026 Mar 27]. Available from: <https://www.wcrf.org/wp-content/uploads/2024/10/Alcoholic-Drinks.pdf>.
29. Caulkins JP. Changes in self-reported cannabis use in the United States from 1979 to 2022. *Addiction*. 2024;119(9):1648-1652. doi:10.1111/add.16519.
30. Garavan H, Bartsch H, Conway K, et al. Recruiting the ABCD sample: design considerations and procedures. *Dev Cogn Neurosci*. 2018;32:16-22. doi:10.1016/j.dcn.2018.04.004.
31. Jernigan TL, Brown SA, Dowling GJ. The Adolescent Brain Cognitive Development Study. *J Res Adolesc*. 2018;28(1):154-156. doi:10.1111/jora.12374.
32. National Institute of Mental Health. Recruitment begins for landmark study of adolescent brain development [Internet]. [cited 2026 Mar 27]. Available from: <https://www.nimh.nih.gov/news/science-updates/2016/recruitment-begins-for-landmark-study-of-adolescent-brain-development>.
33. National Institutes of Health. About the All of Us research program [Internet]. [cited 2026 Mar 27]. Available from: <https://www.joinallofus.org/>.
34. Adams S. psychopharmacology of tobacco and alcohol comorbidity: a review of current evidence. *Curr Addict Rep*. 2017;4(1):25-34. doi:10.1007/s40429-017-0129-z.
35. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. *Behav Genet*. 1995;25(2):95-101. doi:10.1007/bf02196920.
36. Dani JA, Harris RA. Nicotine addiction and comorbidity with alcohol abuse and mental illness. *Nat Neurosci*. 2005;8(11):1465-1470. doi:10.1038/nn1580.
37. Altman CM, Marlin BJ, Charalambakis NE, et al. The next 50 years of neuroscience. *J Neurosci*. 2020;40(1):101-106. doi:10.1523/jneurosci.0744-19.2019.
38. Mišić B, Sporns O. From regions to connections and networks: new bridges between brain and behavior. *Curr Opin Neurobiol*. 2016;40:1-7. doi:10.1016/j.conb.2016.05.003.
39. Lee J, Kim SW, Kim KT. Region-specific characteristics of astrocytes and microglia: a possible involvement in aging and diseases. *Cells*. 2022;11(12). doi:10.3390/cells11121902.
40. Davis S, Zhu J. Substance abuse and neurotransmission. *Adv Pharmacol*. 2022;93:403-441.
41. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760-773. doi:10.1016/S2215-0366(16)00104-8.
42. Folker A, Peviani KM, Deater-Deckard K, Bickel WK, Steinberg L, Casas B, Kim-Spoon J. Negative affect, sensation seeking, and adolescent substance use development: the moderating role of executive function. *J Youth Adolesc*. 2024;53(11):2654-2668. doi:10.1007/s10964-024-02065-9.
43. Semaan A, Khan MK. Neurobiology of addiction. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. [cited 2026 Mar 27]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK597351>.

44. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*. 2002;159(10):1642-52. doi:10.1176/appi.ajp.159.10.1642.
45. Moeller SJ, Konova AB, Parvaz MA, Tomasi D, Lane RD, Fort C, Goldstein RZ. Functional, structural, and emotional correlates of impaired insight in cocaine addiction. *JAMA Psychiatry*. 2014;71(1):61-70. doi:10.1001/jamapsychiatry.2013.2833.
46. Tizabi Y, Bai L, Copeland RL, Taylor RE. Combined effects of systemic alcohol and nicotine on dopamine release in the nucleus accumbens shell. *Alcohol Alcohol*. 2007;42(5):413-416. doi:10.1093/alcalc/agg057.
47. Crummy EA, O'Neal TJ, Baskin BM, Ferguson SM. One is not enough: understanding and modeling polysubstance use. *Front Neurosci*. 2020;14:569. doi:10.3389/fnins.2020.00569.
48. Bailey AJ, Farmer EJ, Finn PR. Patterns of polysubstance use and simultaneous co-use in high risk young adults. *Drug Alcohol Depend*. 2019;205:107656. doi:10.1016/j.drugalcdep.2019.107656.
49. Connor JP, Gullo MJ, White A, Kelly AB. Polysubstance use: diagnostic challenges, patterns of use and health. *Curr Opin Psychiatry*. 2014;27(4):269-75. doi:10.1097/yco.000000000000069.
50. Pan Y, Feaster DJ, Odom G, et al. Specific polysubstance use patterns predict relapse among patients entering opioid use disorder treatment. *Drug Alcohol Depend Rep*. 2022;5. doi:10.1016/j.dadr.2022.100128.
51. Kamens HM, Flarend G, Horton WJ. The role of nicotinic receptors in alcohol consumption. *Pharmacol Res*. 2023;190:106705. doi:10.1016/j.phrs.2023.106705.
52. Nocente R, Vitali M, Balducci G, Enea D, Kranzler HR, Ceccanti M. Varenicline and neuronal nicotinic acetylcholine receptors: a new approach to the treatment of co-occurring alcohol and nicotine addiction? *Am J Addict*. 2013;22(5):453-9. doi:10.1111/j.1521-0391.2013.12037.x.
53. Worley J. The role of pleasure neurobiology and dopamine in mental health disorders. *J Psychosoc Nurs Ment Health Serv*. 2017;55(9):17-21. doi:10.3928/02793695-20170818-09.
54. Becker HC, Griffin WC, Lopez MF. Chapter 18 - Neuroadaptive changes that result from chronic drug exposure. In: Miller PM, editor. *Biological Research on Addiction*. Academic Press; 2013:169-178.
55. Funk D, Marinelli PW, Lê AD. Biological processes underlying co-use of alcohol and nicotine: neuronal mechanisms, cross-tolerance, and genetic factors. *Alcohol Res Health*. 2006;29(3):186-92.
56. Melis M, Spiga S, Diana M. The dopamine hypothesis of drug addiction: hypodopaminergic state. *Int Rev Neurobiol*. 2005;63:101-54. doi:10.1016/s0074-7742(05)63005-x.
57. Morel C, Montgomery S, Han MH. Nicotine and alcohol: the role of midbrain dopaminergic neurons in drug reinforcement. *Eur J Neurosci*. 2019;50(3):2180-2200. doi:10.1111/ejn.14160.
58. Koob GF. Animal models of drug addiction. In: Brownell KD, Gold MS, editors. *Food and Addiction: A Comprehensive Handbook*. Oxford University Press; 2012:0.
59. Goldberg LR, Gould TJ. Genetic influences impacting nicotine use and abuse during adolescence: Insights from human and rodent studies. *Brain Res Bull*. 2022;187:24-38. doi:10.1016/j.brainresbull.2022.06.007.
60. Peltz G, Tan Y. What have we learned (or expect to) from analysis of murine genetic models related to substance use disorders? *Front Psychiatry*. 2021;12:793961. doi:10.3389/fpsy.2021.793961.
61. Elvig SK, McGinn MA, Smith C, Arends MA, Koob GF, Vendruscolo LF. Tolerance to alcohol: a critical yet understudied factor in alcohol addiction. *Pharmacol Biochem Behav*. 2021;204:173155. doi:10.1016/j.pbb.2021.173155.
62. Fisher ML, Pauly JR, Froeliger B, Turner JR. Translational research in nicotine addiction. *Cold Spring Harb Perspect Med*. 2021;11(6). doi:10.1101/cshperspect.a039776.
63. Hopf FW, Lesscher HM. Rodent models for compulsive alcohol intake. *Alcohol*. May 2014;48(3):253-64. doi:10.1016/j.alcohol.2014.03.001.
64. Ellenbroek B, Youn J. Rodent models in neuroscience research: is it a rat race? *Dis Model Mech*. 2016;9(10):1079-1087. doi:10.1242/dmm.026120.
65. Hauser SR, Waeiss RA, Deehan GA, Jr., Engleman EA, Bell RL, Rodd ZA. Adolescent alcohol and nicotine exposure alters the adult response to alcohol use. *Adv Drug Alcohol Res*. 2023;3:11880. doi:10.3389/adar.2023.11880.
66. McCabe SE, Schulenberg JE, Schepis TS, McCabe VV, Veliz PT. Longitudinal analysis of substance use disorder symptom severity at age 18 years and substance use disorder in adulthood. *JAMA Netw Open*. 2022;5(4):e225324. doi:10.1001/jamanetworkopen.2022.5324.
67. Steinfeld MR, Torregrossa MM. Consequences of adolescent drug use. *Transl Psychiatry*. 2023;13(1):313. doi:10.1038/s41398-023-02590-4.
68. Kasprzyk J, Piekoszewski W, Tezyk A, Kulza M, Florek E. Effects of excessive alcohol drinking on nicotine biotransformation in rats. *Sci Rep*. 2022;12(1):11066. doi:10.1038/s41598-022-15199-2.

69. Clark A, Little HJ. Interactions between low concentrations of ethanol and nicotine on firing rate of ventral tegmental dopamine neurones. *Drug Alcohol Depend.* 2004;75(2):199-206. doi:10.1016/j.drugalcdep.2004.03.001.
70. Miller CN, Kamens HM. The role of nicotinic acetylcholine receptors in alcohol-related behaviors. *Brain Research Bulletin.* 2020;163:135-142. doi:10.1016/j.brainresbull.2020.07.017.
71. Davis TJ, de Fiebre CM. Alcohol's actions on neuronal nicotinic acetylcholine receptors. *Alcohol Res Health.* 2006;29(3):179-185.
72. Abrahao KP, Salinas AG, Lovinger DM. Alcohol and the brain: neuronal molecular targets, synapses, and circuits. *Neuron.* 2017;96(6):1223-1238. doi:10.1016/j.neuron.2017.10.032.
73. Chatterjee S, Bartlett S. Neuronal nicotinic acetylcholine receptors as pharmacotherapeutic targets for the treatment of alcohol use disorders. *CNS Neurol Disord Drug Targets.* 2010;9(1):60-76. doi:10.2174/187152710790966597.
74. Ericson M, Molander A, Löf E, Engel JA, Söderpalm B. Ethanol elevates accumbal dopamine levels via indirect activation of ventral tegmental nicotinic acetylcholine receptors. *Eur J Pharmacol.* 2003;467(1-3):85-93. doi:10.1016/S0014-2999(03)01564-4.
75. McLaughlin I, Dani JA, De Biasi M. The medial habenula and interpeduncular nucleus circuitry is critical in addiction, anxiety, and mood regulation. *J Neurochem.* 2017;142:130-143. doi:10.1111/jnc.14008.
76. Perez E, Quijano-Cardé N, De Biasi M. Nicotinic mechanisms modulate ethanol withdrawal and modify time course and symptoms severity of simultaneous withdrawal from alcohol and nicotine. *Neuropsychopharmacol.* 2015;40(10):2327-2336. doi:10.1038/npp.2015.80.
77. Tervo-Clemmens B, Quach A, Calabro FJ, Foran W, Luna B. Meta-analysis and review of functional neuroimaging differences underlying adolescent vulnerability to substance use. *Neuroimage.* 2020;209:116476. doi:10.1016/j.neuroimage.2019.116476.
78. Gurka KK, Burris HH, Ciciolla L, et al. Assessment of maternal health and behavior during pregnancy in the HEALTHY Brain and Child Development Study: rationale and approach. *Dev Cogn Neurosci.* 2025;71:101494. doi:10.1016/j.dcn.2024.101494.
79. Volkow ND, Gordon JA, Freund MP. The Healthy Brain and Child Development Study-shedding light on opioid exposure, COVID-19, and health disparities. *JAMA Psychiatry.* 2021;78(5):471-72. doi:10.1001/jamapsychiatry.2020.3803.
80. Ceceli AO, Bradberry CW, Goldstein RZ. The neurobiology of drug addiction: cross-species insights into the dysfunction and recovery of the prefrontal cortex. *Neuropsychopharmacol.* 2022;47(1):276-91. doi:10.1038/s41386-021-01153-9.
81. Thompson PM, Jahanshad N, Ching CRK, et al. ENIGMA and global neuroscience: a decade of large-scale studies of the brain in health and disease across more than 40 countries. *Transl Psychiatry.* 2020;10(1):100. doi:10.1038/s41398-020-0705-1.
82. Zilverstand A, Huang AS, Alia-Klein N, Goldstein RZ. Neuroimaging impaired response inhibition and salience attribution in human drug addiction: a systematic review. *Neuron.* 2018;98(5):886-903. doi:10.1016/j.neuron.2018.03.048.
83. Maxwell AM, Brucar LR, Zilverstand A. A systematic review of sex/gender differences in the multi-dimensional neurobiological mechanisms in addiction and their relevance to impulsivity. *Curr Addict Rep.* 2023;10(4):770-92. doi:10.1007/s40429-023-00529-9.
84. Drossel G, Heilbronner SR, Zimmermann J, Zilverstand A. Neuroimaging of the effects of drug exposure or self-administration in rodents: a systematic review. *Neurosci Biobehav Rev.* 2024;164:105823. doi:10.1016/j.neubiorev.2024.105823.
85. Liu J, Claus ED, Calhoun VD, Hutchison KE. Brain regions affected by impaired control modulate responses to alcohol and smoking cues. *J Stud Alcohol Drugs.* 2014;75(5):808-816. doi:10.15288/jsad.2014.75.808.
86. Chang Y, Thornton V, Chaloehtom A, et al. Investigating the relationship between smoking behavior and global brain volume. *Biol Psychiatry Glob Open Sci.* 2024;4(1):74-82. doi:10.1016/j.bpsgos.2023.09.006.
87. Chye Y, Mackey S, Gutman BA, et al. Subcortical surface morphometry in substance dependence: an ENIGMA addiction working group study. *Addiction Biology.* 2020;25(6):e12830. doi:10.1111/adb.12830.
88. Gray JC, Thompson M, Bachman C, Owens MM, Murphy M, Palmer R. Associations of cigarette smoking with gray and white matter in the UK Biobank. *Neuropsychopharmacol.* 2020;45(7):1215-22. doi:10.1038/s41386-020-0630-2.
89. Logtenberg E, Overbeek MF, Pasman JA, et al. Investigating the causal nature of the relationship of subcortical brain volume with smoking and alcohol use. *Br J Psychiatry.* 2022;221(1):377-385. doi:10.1192/bjp.2021.81.

90. Kwako LE, Schwandt ML, Ramchandani VA, et al. Neurofunctional domains derived from deep behavioral phenotyping in alcohol use disorder. *Am J Psychiatry*. 2019;176(9):744-753. doi:10.1176/appi.ajp.2018.18030357.
91. Drossel G, Brucar LR, Rawls E, Hendrickson TJ, Zilverstand A. Subtypes in addiction and their neurobehavioral profiles across three functional domains. *Transl Psychiatry*. 2023;13(1):127. doi:10.1038/s41398-023-02426-1.
92. Medline Plus, National Library of Medicine. What is heritability? [Internet]. [cited 2026 Mar 27]. Available from: <https://medlineplus.gov/genetics/understanding/inheritance/heritability>.
93. Moore DS, Shenk D. The heritability fallacy. *Wiley Interdiscip Rev Cogn Sci*. 2017;8(1-2). doi:10.1002/wcs.1400.
94. Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. *Nat Rev Genet*. 2013;14(2):139-49. doi:10.1038/nrg3377.
95. Salvatore JE, Cho SB, Dick DM. Genes, environments, and sex differences in alcohol research. *J Stud Alcohol Drugs*. 2017;78(4):494-501. doi:10.15288/jsad.2017.78.494.
96. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychol Med*. 2015;45(5):1061-1072. doi:10.1017/S0033291714002165.
97. Li MD, Cheng R, Ma JZ, Swan GE. A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins: Genetic and environmental effects on smoking behavior. *Addiction*. 2003;98(1):23-31. doi:10.1046/j.1360-0443.2003.00295.x.
98. Deak JD, Johnson EC. Genetics of substance use disorders: a review. *Psychol Med*. 2021;51(13):2189-2200. doi:10.1017/s0033291721000969.
99. Liu IC, Blacker DL, Xu R, Fitzmaurice G, Lyons MJ, Tsuang MT. Genetic and environmental contributions to the development of alcohol dependence in male twins. *Arch Gen Psychiatry*. 2004;61(9):897. doi:10.1001/archpsyc.61.9.897.
100. Sartor CE, Agrawal A, Lynskey MT, Bucholz KK, Heath AC. Genetic and environmental influences on the rate of progression to alcohol dependence in young women. *Alcoholism Clin Exp Res*. 2008;32(4):632-638. doi:10.1111/j.1530-0277.2008.00621.x.
101. Bjork JM, Straub LK, Provost RG, Neale MC. The ABCD study of neurodevelopment: Identifying neurocircuit targets for prevention and treatment of adolescent substance abuse. *Curr Treat Options Psychiatry*. 2017;4(2):196-209. doi:10.1007/s40501-017-0108-y.
102. Do EK, Prom-Wormley EC, Eaves LJ, Silberg JL, Miles DR, Maes HH. Genetic and environmental influences on smoking behavior across adolescence and young adulthood in the Virginia Twin Study of Adolescent Behavioral Development and the transitions to substance abuse follow-up. *Twin Res Hum Genet*. 2015;18(1):43-51. doi:10.1017/thg.2014.78.
103. Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch Gen Psychiatry*. 2003;60(12):1256-64. doi:10.1001/archpsyc.60.12.1256.
104. Hopfer CJ, Crowley TJ, Hewitt JK. Review of twin and adoption studies of adolescent substance use. *J Am Acad Child Adolesc Psychiatry*. 2003;42(6):710-19. doi:10.1097/01.CHI.0000046848.56865.54.
105. Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. *Nat Rev Genet*. 2005;6(7):521-32. doi:10.1038/nrg1635.
106. Schuckit MA. A brief history of research on the genetics of alcohol and other drug use disorders. *J Stud Alcohol Drugs Suppl*. 2014;75(17):59-67. doi:10.15288/jsads.2014.s17.59.
107. Borecki IB, Province MA. Linkage and association: basic concepts. *Adv Genet*. 2008;60:51-74. doi:10.1016/s0065-2660(07)00403-8.
108. Hall FS, Chen Y, Resendiz-Gutierrez F. The streetlight effect: reappraising the study of addiction in light of the findings of genome-wide association studies. *Brain Behav Evol*. 2020 2020;95(5):230-46. doi:10.1159/000516169.
109. Ioannidis JP. Genetic associations: false or true? *Trends Mol Med*. 2003;9(4):135-8. doi:10.1016/s1471-4914(03)00030-3.
110. Hellwege JN, Keaton JM, Giri A, Gao X, Velez Edwards DR, Edwards TL. Population stratification in genetic association studies. *Curr Protoc Hum Genet*. 2017;95:1.22.1-1.22.23. doi:10.1002/cphg.48.
111. Dick DM, Agrawal A, Keller MC, et al. Candidate gene-environment interaction research: reflections and recommendations. *Perspect Psychol Sci*. 2015;10(1):37-59. doi:10.1177/1745691614556682.
112. Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry*. 2011;168(10):1041-9. doi:10.1176/appi.ajp.2011.11020191.

113. Olfson E, Bierut LJ. Convergence of genome-wide association and candidate gene studies for alcoholism. *Alcohol Clin Exp Res*. 2012;36(12):2086-94. doi:10.1111/j.1530-0277.2012.01843.x.
114. Siontis KC, Patsopoulos NA, Ioannidis JP. Replication of past candidate loci for common diseases and phenotypes in 100 genome-wide association studies. *Eur J Hum Genet*. 2010;18(7):832-7. doi:10.1038/ejhg.2010.26.
115. Thomas DC, Casey G, Conti DV, Haile RW, Lewinger JP, Stram DO. Methodological issues in multistage genome-wide association studies. *Stat Sci*. 2009;24(4):414-429. doi:10.1214/09-sts288.
116. Abdellaoui A, Yengo L, Verweij KJH, Visscher PM. 15 years of GWAS discovery: realizing the promise. *Am J Hum Genet*. 2023;110(2):179-194. doi:10.1016/j.ajhg.2022.12.011.
117. Stranger BE, Stahl EA, Raj T. Progress and promise of genome-wide association studies for human complex trait genetics. *Genetics*. 2011;187(2):367-83. doi:10.1534/genetics.110.120907.
118. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J. 10 Years of GWAS discovery: biology, function, and translation. *Am J Hum Genet*. 2017;101(1):5-22. doi:10.1016/j.ajhg.2017.06.005.
119. Gerring ZF, Thorp JG, Treur JL, Verweij KJH, Derks EM. The genetic landscape of substance use disorders. *Mol Psychiatry*. 2024;29(11):3694-3705. doi:10.1038/s41380-024-02547-z.
120. National Academies of Sciences, Engineering, and Medicine. Using population descriptors in genetics and genomics research: a new framework for an evolving field. Washington, DC: National Academies Press; 2023.
121. Linder JE, Bastarache L, Hughey JJ, Peterson JF. the role of electronic health records in advancing genomic medicine. *Annu Rev Genomics Hum Genet*. 2021;22:219-238. doi:10.1146/annurev-genom-121120-125204.
122. Reales G, Wallace C. Sharing GWAS summary statistics results in more citations. *Commun Biol*. 2023;6(1):116. doi:10.1038/s42003-023-04497-8.
123. First MB, Clarke DE, Yousif L, Eng AM, Gogtay N, Appelbaum PS. DSM-5-TR: rationale, process, and overview of changes. *Psychiatr Serv*. 2023;74(8):869-875. doi:10.1176/appi.ps.20220334.
124. Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry*. 2013;170(8):834-51. doi:10.1176/appi.ajp.2013.12060782.
125. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K-O. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Addiction*. 1991;86(9):1119-1127. doi:10.1111/j.1360-0443.1991.tb01879.x.
126. Lessov-Schlaggar CN, Pergadia ML, Khroyan TV, Swan GE. Genetics of nicotine dependence and pharmacotherapy. *Biochem Pharmacol*. 2008;75(1):178-95. doi:10.1016/j.bcp.2007.08.018.
127. Agrawal A, Freedman ND, Cheng YC, et al. Measuring alcohol consumption for genomic meta-analyses of alcohol intake: opportunities and challenges. *Am J Clin Nutr*. 2012;95(3):539-47. doi:10.3945/ajcn.111.015545.
128. Deak JD, Miller AP, Gizer IR. Genetics of alcohol use disorder: a review. *Curr Opin Psychol*. 2019;27:56-61. doi:10.1016/j.copsyc.2018.07.012.
129. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction*. 1993;88(6):791-804. doi:10.1111/j.1360-0443.1993.tb02093.x.
130. Kember RL, Vickers-Smith R, Zhou H, et al. Genetic underpinnings of the transition from alcohol consumption to alcohol use disorder: shared and unique genetic architectures in a cross-ancestry sample. *AJP*. 2023;180(8):584-593. doi:10.1176/appi.ajp.21090892.
131. Gupta I, Dandavate R, Gupta P, Agrawal V, Kapoor M. Recent advances in genetic studies of alcohol use disorders. *Curr Genet Med Rep*. 2020;8(2):27-34. doi:10.1007/s40142-020-00185-9.
132. Tyndale RF. Genetics of alcohol and tobacco use in humans. *Ann Med*. 2003;35(2):94-121. doi:10.1080/07853890310010014.
133. Turley P, Walters RK, Maghzian O, et al. Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat Genet*. 2018;50(2):229-237. doi:10.1038/s41588-017-0009-4.
134. Fowler T, Lifford K, Shelton K, et al. Exploring the relationship between genetic and environmental influences on initiation and progression of substance use. *Addiction*. 2007;102(3):413-22. doi:10.1111/j.1360-0443.2006.01694.x.
135. Quach BC, Bray MJ, Gaddis NC, et al. Expanding the genetic architecture of nicotine dependence and its shared genetics with multiple traits. *Nat Commun*. 2020;11(1):5562. doi:10.1038/s41467-020-19265-z.
136. Saccone SF, Hinrichs AL, Saccone NL, et al. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Human Molecular Genetics*. 2007;16(1):36-49. doi:10.1093/hmg/ddl438.

137. Chadi N, Hadland SE, Harris SK. Understanding the implications of the "vaping epidemic" among adolescents and young adults: A call for action. *Subst Abus.* 2019;40(1):7-10. doi:10.1080/08897077.2019.1580241.
138. Jamal A, Park-Lee E, Birdsey J, et al. Tobacco product use among middle and high school students - National Youth Tobacco Survey, United States, 2024. *MMWR Morb Mortal Wkly Rep.* 2024;73(41):917-924. doi:10.15585/mmwr.mm7341a2.
139. Edenberg HJ. The Genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Res Health.* 2007;30(1):5-13.
140. Hukkanen J, Jacob P, 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev.* 2005;57(1):79-115. doi:10.1124/pr.57.1.3.
141. Mwenifumbo JC, Tyndale RF. Molecular genetics of nicotine metabolism. In: Henningfield JE, London ED, Pogun S, editors. *Nicotine Psychopharmacology.* Springer; 2009:235-259.
142. Wen L, Jiang K, Yuan W, Cui W, Li MD. Contribution of variants in CHRNA5/A3/B4 gene cluster on chromosome 15 to tobacco smoking: from genetic association to mechanism. *Mol Neurobiol.* 2016;53(1):472-484. doi:10.1007/s12035-014-8997-x.
143. Saccone NL, Culverhouse RC, Schwantes-An T-H, et al. Multiple independent loci at chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD. *PLoS Genet.* 2010;6(8). doi:10.1371/journal.pgen.1001053.
144. Tamminen A, Herder P, Li P, Esch C, Laughlin JR, Akk G, Stitzel JA. Impact of human D398N single nucleotide polymorphism on intracellular calcium response mediated by $\alpha 3\beta 4\alpha 5$ nicotinic acetylcholine receptors. *Neuropharmacology.* 2012;63(6):1002-11. doi:10.1016/j.neuropharm.2012.07.022.
145. Wang JC, Grucza R, Cruchaga C, et al. Genetic variation in the CHRNA5 gene affects mRNA levels and is associated with risk for alcohol dependence. *Mol Psychiatry.* 2009;14(5):501-10.
146. Ehringer MA, Clegg HV, Collins AC, et al. Association of the neuronal nicotinic receptor beta2 subunit gene (CHRNA2) with subjective responses to alcohol and nicotine. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144B(5):596-604. doi:10.1002/ajmg.b.30464.
147. Hoft NR, Corley RP, McQueen MB, Huizinga D, Menard S, Ehringer MA. SNPs in CHRNA6 and CHRNA3 are associated with alcohol consumption in a nationally representative sample. *Genes Brain Behav.* 2009;8(6):631-637. doi:10.1111/j.1601-183X.2009.00495.x.
148. Schlaepfer IR, Hoft NR, Collins AC, et al. The CHRNA5/A3/B4 gene cluster variability as an important determinant of early alcohol and tobacco initiation in young adults. *Biol Psychiatry.* 2008;63(11):1039-46. doi:10.1016/j.biopsych.2007.10.024.
149. Sherva R, Kranzler HR, Yu Y, et al. Variation in nicotinic acetylcholine receptor genes is associated with multiple substance dependence phenotypes. *Neuropsychopharmacol.* 2010;35(9):1921-1931. doi:10.1038/npp.2010.64.
150. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: An $\alpha 4\beta 2$ Nicotinic receptor partial agonist for smoking cessation. *J Med Chem.* 2005;48(10):3474-3477. doi:10.1021/jm050069n.
151. Brynildsen JK, Blendy JA. Linking the CHRNA5 SNP to drug abuse liability: from circuitry to cellular mechanisms. *Neuropharmacology.* 2021;186:108480. doi:10.1016/j.neuropharm.2021.108480.
152. Reed E, Nunez S, Kulp D, Qian J, Reilly MP, Foulkes AS. A guide to genome-wide association analysis and post-analytic interrogation. *Stat Med.* 2015;34(28):3769-92. doi:10.1002/sim.6605.
153. Psychiatric Genomics Consortium. Psychiatric Genomics Consortium - About us [Internet]. [cited 2026 Mar 27]. Available from: <https://pgc.unc.edu/about-us>.
154. Psychiatric Genomics Consortium. For researchers - working groups - substance use disorders [Internet]. [cited 2026 Mar 27]. Available from: <https://pgc.unc.edu/for-researchers/working-groups/substance-use-disorders-working-group>.
155. Levings D, Shaw KE, Lacher SE. Genomic resources for dissecting the role of non-protein coding variation in gene-environment interactions. *Toxicology.* 2020;441:152505. doi:10.1016/j.tox.2020.152505.
156. Dingel MJ, Ostergren J, Koenig BA, McCormick J. "Why did I get that part of you?" Understanding addiction genetics through family history. *Public Underst Sci.* 2019;28(1):53-67. doi:10.1177/0963662518785350.
157. Driver MN, Kuo SI, Dick DM. Returning complex genetic risk information to promote better health-related behaviors: a commentary of the literature and suggested next steps. *Transl Behav Med.* 2023;13(2):115-119. doi:10.1093/tbm/ibac071.
158. Lu Z, Gopalan S, Yuan D, Conti DV, Pasaniuc B, Gusev A, Mancuso N. Multi-ancestry fine-mapping improves precision to identify causal genes in transcriptome-wide association studies. *Am J Hum Genet.* 2022;109(8):1388-1404. doi:10.1016/j.ajhg.2022.07.002.

159. Chen F, Wang X, Jang SK, et al. Multi-ancestry transcriptome-wide association analyses yield insights into tobacco use biology and drug repurposing. *Nat Genet.* 2023;55(2):291-300. doi:10.1038/s41588-022-01282-x.
160. Chen LS, Baker TB, Ramsey A, Amos CI, Bierut LJ. Genomic medicine to reduce tobacco and related disorders: Translation to precision prevention and treatment. *Addict Neurosci.* 2023;7. doi:10.1016/j.addicn.2023.100083.
161. Driver MN, Kuo SI, Austin J, Dick DM. Integrating theory with education about genetic risk for alcohol use disorder: the effects of a brief online educational tool on elements of the Health Belief Model. *Complex Psychiatry.* 2023;9(1-4):89-99. doi:10.1159/000530222.
162. Driver MN, Kuo SI, Dron JS, Austin J, Dick DM. The impact of receiving polygenic risk scores for alcohol use disorder on psychological distress, risk perception, and intentions to reduce drinking. *Am J Med Genet B Neuropsychiatr Genet.* 2023;192(5-6):93-101. doi:10.1002/ajmg.b.32933.
163. Lohoff FW. Pharmacotherapies and personalized medicine for alcohol use disorder: a review. *Pharmacogenomics.* 2020;21(15):1117-1138. doi:10.2217/pgs-2020-0079.
164. Benowitz NL, Pomerleau OF, Pomerleau CS, Jacob P, 3rd. Nicotine metabolite ratio as a predictor of cigarette consumption. *Nicotine Tob Res.* 2003;5(5):621-4. doi:10.1080/1462220031000158717.
165. Allenby CE, Boylan KA, Lerman C, Falcone M. Precision medicine for tobacco dependence: development and validation of the nicotine metabolite ratio. *J Neuroimmune Pharmacol.* 2016;11(3):471-483. doi:10.1007/s11481-016-9656-y.
166. Murphy SE. Biochemistry of nicotine metabolism and its relevance to lung cancer. *J Biol Chem.* 2021;296:100722. doi:10.1016/j.jbc.2021.100722.
167. U.S. Department of Health and Human Services. *Smoking Cessation. A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2020.
168. Chen L-S, Horton A, Bierut L. Pathways to precision medicine in smoking cessation treatments. *Neuroscience Letters.* 2018;669:83-92. doi:10.1016/j.neulet.2016.05.033.
169. Lerman C, Schnoll RA, Hawk LW, et al. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. *The Lancet Respiratory Medicine.* 2015;3(2):131-138. doi:10.1016/S2213-2600(14)70294-2.
170. Murphy SE. Nicotine metabolism and smoking: ethnic differences in the role of P450 2A6. *Chem Res Toxicol.* 2017;30(1):410-419. doi:10.1021/acs.chemrestox.6b00387.
171. Murphy SE, Park SL, Balbo S, et al. Tobacco biomarkers and genetic/epigenetic analysis to investigate ethnic/racial differences in lung cancer risk among smokers. *NPJ Precis Oncol.* 2018;2:17. doi:10.1038/s41698-018-0057-y.
172. Park SL, Tiirikainen MI, Patel YM, Wilkens LR, Stram DO, Le Marchand L, Murphy SE. Genetic determinants of CYP2A6 activity across racial/ethnic groups with different risks of lung cancer and effect on their smoking intensity. *Carcinogenesis.* 2016;37(3):269-279. doi:10.1093/carcin/bgw012.
173. Stram DO, Park SL, Haiman CA, Murphy SE, Patel Y, Hecht SS, Le Marchand L. Racial/Ethnic differences in lung cancer incidence in the Multiethnic Cohort Study: an update. *J Natl Cancer Inst.* 2019;111(8):811-819. doi:10.1093/jnci/djy206.
174. Tanner JA, Tyndale RF. Variation in CYP2A6 activity and personalized medicine. *J Pers Med.* 2017;7(4). doi:10.3390/jpm7040018.
175. Chen LS, Horton A, Bierut L. Pathways to precision medicine in smoking cessation treatments. *Neurosci Lett.* 2018;669:83-92. doi:10.1016/j.neulet.2016.05.033.
176. Chen LS, Baker TB, Jorenby D, et al. Genetic variation (CHRNA5), medication (combination nicotine replacement therapy vs. varenicline), and smoking cessation. *Drug Alcohol Depend.* 2015;154:278-82. doi:10.1016/j.drugalcdep.2015.06.022.
177. Chen LS, Baker TB, Miller JP, et al. Genetic Variant in CHRNA5 and response to varenicline and combination nicotine replacement in a randomized placebo-controlled trial. *Clin Pharmacol Ther.* 2020;108(6):1315-25. doi:10.1002/cpt.1971.
178. Chen LS, Baker TB, Piper ME, et al. Interplay of genetic risk factors (CHRNA5-CHRNA3-CHRNA4) and cessation treatments in smoking cessation success. *Am J Psychiatry.* 2012;169(7):735-42. doi:10.1176/appi.ajp.2012.11101545.
179. Chen LS, Hung RJ, Baker T, et al. CHRNA5 risk variant predicts delayed smoking cessation and earlier lung cancer diagnosis--a meta-analysis. *Natl Cancer Inst.* 2015;107(5):djv100.

180. Jones SK, Wolf BJ, Froeliger B, Wallace K, Carpenter MJ, Alberg AJ. A systematic review of genetic variation within nicotinic acetylcholine receptor genes and cigarette smoking cessation. *Drug Alcohol Depend.* 2022;239:109596. doi:10.1016/j.drugalcdep.2022.109596.
181. Hartwell EE, Feinn R, Morris PE, et al. Systematic review and meta-analysis of the moderating effect of rs1799971 in OPRM1, the mu-opioid receptor gene, on response to naltrexone treatment of alcohol use disorder. *Addiction.* 2020;115(8):1426-1437. doi:10.1111/add.14975.
182. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. *Brit J Clinical Pharma.* 2014;77(2):315-323. doi:10.1111/bcp.12070.
183. Hartwell EE, Kranzler HR. Pharmacogenetics of alcohol use disorder treatments: an update. *Expert Opin Drug Metab Toxicol.* 2019;15(7):553-564. doi:10.1080/17425255.2019.1628218.
184. Manhapra A, Chakraborty A, Arias AJ. Topiramate pharmacotherapy for alcohol use disorder and other addictions: a narrative review. *J Addict Med.* 2019;13(1):7-22. doi:10.1097/ADM.0000000000000443.
185. Blodgett JC, Del Re AC, Maisel NC, Finney JW. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcoholism Clin Exp Res.* 2014;38(6):1481-1488. doi:10.1111/acer.12411.
186. Brockway DF, Crowley NA. Emerging pharmacological targets for alcohol use disorder. *Alcohol.* 2024;121:103-114. doi:10.1016/j.alcohol.2024.07.007.
187. Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry.* 2022;79(10):953-962. doi:10.1001/jamapsychiatry.2022.2096.
188. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol.* 2015;29(3):289-99. doi:10.1177/0269881114565144.
189. Krebs TS, Johansen P. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. *J Psychopharmacol.* 2012;26(7):994-1002. doi:10.1177/0269881112439253.
190. Bordia T, Hrachova M, Chin M, McIntosh JM, Quik M. Varenicline is a potent partial agonist at $\alpha 6\beta 2^*$ nicotinic acetylcholine receptors in rat and monkey striatum. *J Pharmacol Exp Ther.* 2012;342(2):327-334. doi:10.1124/jpet.112.194852.
191. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors. *Mol Pharmacol.* 2006;70(3):801-805. doi:10.1124/mol.106.025130.
192. Mineur YS, Picciotto MR. Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. *Trends Pharmacol Sci.* 2010;31(12):580-586. doi:10.1016/j.tips.2010.09.004.
193. Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL. Varenicline decreases alcohol consumption in heavy-drinking smokers. *Psychopharmacology (Berl).* 2012;223(3):299-306. doi:10.1007/s00213-012-2717-x.
194. Litten RZ, Ryan ML, Fertig JB, et al. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *J Addict Med.* 2013;7(4):277-86. doi:10.1097/ADM.0b013e31829623f4.
195. Yardley MM, Mirbaba MM, Ray LA. Pharmacological options for smoking cessation in heavy-drinking smokers. *CNS Drugs.* 2015;29(10):833-845. doi:10.1007/s40263-015-0284-5.
196. Soyka M, Rösner S. Modern pharmacotherapy guidance for treating alcohol use disorders. *Expert Opin Pharmacother.* 2025 Feb;26(2):147-156.
197. Phimarn W, Sakhancord R, Paitoon P, Saramunee K, Sungthong B. Efficacy of varenicline in the treatment of alcohol dependence: an updated meta-analysis and meta-regression. *Int J Environ Res Public Health.* 2023;20(5). doi:10.3390/ijerph20054091.
198. Gou Y, Schwartz MW. How should we think about the unprecedented weight loss efficacy of incretin-mimetic drugs? *J Clin Invest.* 2023;133(19). doi:10.1172/jci174597.
199. van Bloemendaal L, Ten Kulve JS, la Fleur SE, Ijzerman RG, Diamant M. Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS. *J Endocrinol.* 2014;221(1):T1-16. doi:10.1530/joe-13-0414.
200. Bremmer MP, Hendershot CS. Social Media as Pharmacovigilance: The potential for patient reports to inform clinical research on glucagon-like peptide 1 (GLP-1) receptor agonists for substance use disorders. *J Stud Alcohol Drugs.* 2024;85(1):5-11. doi:10.15288/jsad.23-00318.
201. Aranäs C, Edvardsson CE, Shevchouk OT, et al. Semaglutide reduces alcohol intake and relapse-like drinking in male and female rats. *EBioMedicine.* 2023;93:104642. doi:10.1016/j.ebiom.2023.104642.
202. Chuong V, Farokhnia M, Khom S, et al. The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission. *JCI Insight.* 2023;8(12). doi:10.1172/jci.insight.170671.

203. Martinelli S, Mazzotta A, Longaroni M, Petrucciani N. Potential role of glucagon-like peptide-1 (GLP-1) receptor agonists in substance use disorder: a systematic review of randomized trials. *Drug Alcohol Depend.* 2024;264:112424. doi:10.1016/j.drugalcdep.2024.112424.
204. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with tobacco use disorder in patients with type 2 diabetes : target trial emulation using real-world data. *Ann Intern Med.* 2024;177(8):1016-1027. doi:10.7326/m23-2718.
205. Hendershot CS, Bremmer MP, Paladino MB, et al. Once-weekly semaglutide in adults with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry.* 2025;82(4):395-405. doi:10.1001/jamapsychiatry.2024.4789.
206. Yammine L, Green CE, Kosten TR, et al. exenatide adjunct to nicotine patch facilitates smoking cessation and may reduce post-cessation weight gain: a pilot randomized controlled trial. *Nicotine Tob Res.* 2021;23(10):1682-1690. doi:10.1093/ntr/ntab066.
207. Yammine L, de Dios C, Suchting R, Green CE, Nielsen DA, Walss-Bass C, Schmitz JM. Exploring predictors of treatment response to GLP-1 receptor agonists for smoking cessation. *Nicotine Tob Res.* 2025. doi:10.1093/ntr/ntaf005.
208. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med.* 2020;12(1):44. doi:10.1186/s13073-020-00742-5.
209. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet.* 2019;51(4):584-591. doi:10.1038/s41588-019-0379-x.
210. Zhang H, Zhan J, Jin J, et al. A new method for multi-ancestry polygenic prediction improves performance across diverse populations. *Nat Genet.* 2023;55(10):1757-1768.
211. Lennon NJ, Kottyan LC, Kachulis C, et al. Selection, optimization and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse U.S. populations. *Nat Med.* 2024;30(2):480-487. doi:10.1038/s41591-024-02796-z.
212. Lai D, Johnson EC, Colbert S, et al. Evaluating risk for alcohol use disorder: Polygenic risk scores and family history. *Alcohol Clin Exp Res.* 2022;46(3):374-383. doi:10.1111/acer.14772.
213. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun.* 2017;8(1):1826. doi:10.1038/s41467-017-01261-5.
214. Watanabe K, Umičević Mirkov M, de Leeuw CA, van den Heuvel MP, Posthuma D. Genetic mapping of cell type specificity for complex traits. *Nat Commun.* 2019;10(1):3222. doi:10.1038/s41467-019-11181-1.
215. Bray MJ, Chen LS, Fox L, et al. Dissecting the genetic overlap of smoking behaviors, lung cancer, and chronic obstructive pulmonary disease: A focus on nicotinic receptors and nicotine metabolizing enzyme. *Genet Epidemiol.* 2020;44(7):748-758. doi:10.1002/gepi.22331.
216. Zhang T, Joubert P, Ansari-Pour N, et al. Genomic and evolutionary classification of lung cancer in never smokers. *Nat Genet.* 2021;53(9):1348-1359. doi:10.1038/s41588-021-00920-0.
217. McKay JD, Truong T, Gaborieau V, et al. A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. *PLoS Genet.* 2011;7(3):e1001333. doi:10.1371/journal.pgen.1001333.
218. Ali J, Sabiha B, Jan HU, Haider SA, Khan AA, Ali SS. Genetic etiology of oral cancer. *Oral Oncology.* 2017;70:23-28. doi:10.1016/j.oraloncology.2017.05.004.
219. Emdin CA, Haas M, Ajmera V, et al. Association of genetic variation with cirrhosis: a multi-trait genome-wide association and gene-environment interaction study. *Gastroenterology.* 2021;160(5):1620-1633.e13. doi:10.1053/j.gastro.2020.12.011.
220. 23andMe Research Team. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. *Nat Genet.* 2019;51(2):245-257. doi:10.1038/s41588-018-0309-3.
221. Deak JD, Levey DF, Wendt FR, et al. Genome-wide investigation of maximum habitual alcohol intake in us veterans in relation to alcohol consumption traits and alcohol use disorder. *JAMA Netw Open.* 2022;5(10):e2238880. doi:10.1001/jamanetworkopen.2022.38880.
222. Deak JD, Zhou H, Galimberti M, et al. Genome-wide association study in individuals of European and African ancestry and multi-trait analysis of opioid use disorder identifies 19 independent genome-wide significant risk loci. *Molecular Psychiatry.* 2022;27(10):3970-3979. doi:10.1038/s41380-022-01709-1.
223. Kranzler HR, Zhou H, Kember RL, et al. Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nat Commun.* 2019;10(1):1499. doi:10.1038/s41467-019-09480-8.

224. Mallard TT, Savage JE, Johnson EC, et al. Item-level genome-wide association study of the Alcohol Use Disorders Identification Test in three population-based cohorts. *AJP*. 2022;179(1):58-70. doi:10.1176/appi.ajp.2020.20091390.
225. Miller AP, Gizer IR. Neurogenetic and multi-omic sources of overlap among sensation seeking, alcohol consumption, and alcohol use disorder. *Addict Biol*. 2024;29(2):e13365. doi:10.1111/adb.13365.
226. Rabinowitz JA, Campos AI, Ong J-S, et al. Shared genetic etiology between cortical brain morphology and tobacco, alcohol, and cannabis use. *Cerebral Cortex*. 2022;32(4):796-807. doi:10.1093/cercor/bhab243.
227. Risner VA, Benca-Bachman CE, Bertin L, et al. Multi-polygenic analysis of nicotine dependence in individuals of European ancestry. *Nicotine Tob Res*. 2021;23(12):2102-2109. doi:10.1093/ntr/ntab105.
228. Wang FL, Hicks BM, Zhou H, Kranzler HR, Gelernter J, Zucker RA. Polygenic risk score for problematic alcohol use predicts heavy drinking and alcohol use disorder symptoms in young adulthood after accounting for adolescent alcohol use and parental alcohol use disorder. *Drug Alcohol Depend*. 2023;248:109909. doi:10.1016/j.drugalcdep.2023.109909.
229. Xu K, Li B, McGinnis KA, et al. Genome-wide association study of smoking trajectory and meta-analysis of smoking status in 842,000 individuals. *Nat Commun*. 2020;11(1):5302. doi:10.1038/s41467-020-18489-3.
230. Zhang H, Grant BF, Hodgkinson CA, et al. Strong and weak cross-inheritance of substance use disorders in a nationally representative sample. *Molecular Psychiatry*. 2022;27(3):1742-1753. doi:10.1038/s41380-021-01370-0.
231. Zhou H, Sealock JM, Sanchez-Roige S, et al. Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nat Neurosci*. 2020;23(7):809-818. doi:10.1038/s41593-020-0643-5.
232. Zhou H, Kalayasiri R, Sun Y, et al. Genome-wide meta-analysis of alcohol use disorder in East Asians. *Neuropsychopharmacol*. 2022;47(10):1791-1797. doi:10.1038/s41386-022-01265-w.
233. Zhou H, Kember RL, Deak JD, et al. Multi-ancestry study of the genetics of problematic alcohol use in over 1 million individuals. *Nat Med*. 2023;29(12):3184-3192. doi:10.1038/s41591-023-02653-5.