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Genetic, Behavioral, and Health-Related Associations in the Journal Drug and Alcohol Dependence: A Scoping Review

DE'JAH RENEE COATES
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Reviewed and approved* by the following:

Alexis R. Santos
Assistant Professor of Human Development and Family Studies, and Demography
Thesis Supervisor

Marie Cross
Assistant Teaching Professor of Biobehavioral Health
Honors Adviser

* Electronic approvals are on file.

ABSTRACT

Substance use among people in the United States and emphasis on genetic influences has been present since early studies on the matter. Further interest in the complex interplay between substance use and genetics, and their joint influence on health, has also been of interest. However, this research is not without limitations, and study conditions, points of interest, and biological arguments vary from study to study. This situation highlights the need for studying the state of the field and the aforementioned variation. This thesis presents a scoping review of research that ties substance use, genetics, and health by focusing on the journal *Drug and Alcohol Dependence*, one of the major outlets in the field. A scoping review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for Scoping Reviews. A total of 120 studies address, in some way, the specific interest of this review. Results suggest wide variation in publication trends, sample demographics, substance use elements, the genetic marker, and study design. The resulting analysis reveals that the current literature encompasses a broad range of gene and behavior interactions and, moderately, acknowledges the health outcomes associated with long-term substance use. Despite the currently available literature covering a broad spectrum of genes, behaviors, and health outcomes, new studies are needed to continue to explore genetic diversity and demographics of the sample and address the limitations of current studies to broaden understanding of substance use disorder as it relates to health outcomes in the field and inform the development of novel treatments.

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Chapter 1

Introduction

Substance use disorder (SUD) is a mental condition affecting the behavior and brain function of an individual and impacting their ability to control their consumption of psychoactive substances such as drugs including tobacco and cannabis, alcohol, and medications such as opioids (NIMH, 2023). In addition to these commonly discussed effects, it impairs the quality of life of those who suffer from it in regard to their vocational, social, and physical functioning (Alexandre, 2011). Due to the functional nature of drugs to influence the body's physiological and biochemical processes, they can have a vast range of pharmacological effects. They can alter neurotransmitter functions, modify the cellular activities, and ultimately affect an individual's mood and overall health. The specific mechanisms of this action are dependent on the type of drug, its intended purpose, and its dosage.

According to the National Center for Drug Abuse Statistics (NCDAS), drug overdoses have claimed the lives of almost one million people in the United States since 1999 (2023). Furthermore, drug overdoses account for 96,700 deaths per year on average, with accidental overdoses becoming a leading cause of death for individuals aged 45 and over in recent years (NCDAS: *Drug Abuse Statistics*, 2023). As the prevalence of drug abuse steadily increases, there is also a need for understanding the genetic, behavioral, and health-related factors that are prevalent in the susceptible population and how the intersection of these factors contributes to the development and progression of SUD.

Historically, tobacco use and nicotine addiction has been a topic of addiction research and drug policy and regulation. However, it has also been regarded as one of the less severe categories of drug use despite current evidence stating that there are no benign forms of tobacco and no safe level of exposure (WHO: *Tobacco*, 2023). Nicotine is highly addictive chemically, most commonly found in the tobacco plant, and is often administered through smoking cigars/cigarettes, inhalation of fine powders, and chewing tobacco. Due to its association with cancer and lung disease related morbidity, cigarette smoking is currently the leading cause of premature death in the United States, making it a growing subject of public health concern (Widysanto et al., 2018). The World Health Organization (WHO) estimated in 2023 that the proportion of the population that consumed tobacco and nicotine in some form was approximately 1.3 billion globally. In the United States, tobacco use accounts for the premature death of 435,000 people annually (WHO: *Tobacco*, 2023). Furthermore, these deaths related to tobacco use are more likely to occur in low to middle-income populations, as 80% of these 1.3 billion tobacco users reside in low-to-middle-income countries (WHO: *Tobacco*, 2023).

Similarly to nicotine consumption, excessive alcohol consumption has become an expected social norm in American society. As noted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), 90% of adults in the U.S. have consumed alcohol in their lifetime, often as part of a celebration, social event, or to accompany a meal. In addition, 40% of these American adults drink in excess when compared to the low-risk guidelines established by the NIAAA (2013). As the consumption of alcohol increases from moderate use and dependency upon the physiological effects of ethanol begins to form, individuals become subject to the effects of alcohol use disorder, or alcoholism. Alcohol use disorder (AUD) and alcoholism are associated with short-term health risks, such as injuries and motor accidents, violence and

assault, alcohol poisoning, and risky sexual behavior, as well as long-term health risks, such as hypertension, cancer, weakening of the immune system, learning and memory issues, anxiety and depression, and social problems (CDC, 2024). Beyond these compromises to quality of life and physical and mental health, AUD is also responsible for approximately three million deaths per year, accounting for 6% of global deaths (NCDAS, 2024). Furthermore, according to the Centers for Disease Control and Prevention, excessive alcohol use in the United States is responsible for 20% of deaths among individuals aged 20-49 years and was found to significantly shorten the lives of these individuals by an average of 23 years (2024).

More recently, research and law enforcement have developed a greater interest in cannabis use. Cannabis products refer to all of the products derived from the *Cannabis sativa* plant including, but not limited to: marijuana (products containing a significant amount of the mind-altering chemical tetrahydrocannabinol, or THC), hemp, and cannabidiol (CBD). Cannabis use disorder (CUD) presents a less severe risk than the aforementioned forms of drug use, making it an emerging public health and biomedical research concern (Connor et al., 2021). Of the 193 million global cannabis users, approximately 10% of them have been diagnosed with CUD (Connor et al., 2021). In the United States, 55 million individuals consistently use marijuana, with a large number of users (24%) being adolescents and young adults (ages 16-24) (NCDAS, 2023). Despite the lack of knowledge regarding the long-term effects of chronic cannabis use, current studies suggest potential risks including cognitive impairment, respiratory issues, and dependence. Thus, continuous research efforts are crucial to understanding the impact of prolonged cannabis use on the physical body and brain function.

Most immediate is the emergence of the opioid epidemic in the United States, which has been categorized as a public health emergency. Over 10 million people participate in

opioid misuse each year, resulting in almost 50,000 deaths per year in the U.S. (NCDAS, 2024). The rise of opioid overdose attributed deaths can be outlined in three distinct waves beginning in the 1990s. According to the Centers for Disease Control, the first wave is characterized by an increase in prescription opioids in 1990, and overdose deaths from prescription overdose misuse began to be observed in 1999 (2013). The second wave began in 2010, when a rapid increase in overdose deaths involving heroin was observed. Most recently, the rise of synthetic opioid use has triggered the third wave of the opioid overdose death phenomenon. In 2013, there was a significant increase in deaths due to fentanyl, heroin, counterfeit pills, and cocaine usage (CDC, 2013).

Genetic Influences on Substance Abuse Susceptibility

Historically, it has been understood that a combination of genetic influence and environmental factors have an effect on behavior. Genetic variation has impacted the ways in which people differ in terms of their intellectual capacity, personality traits, mental health, and physical health. Predisposition to health outcomes, behavioral outcomes, and specific diseases and conditions, such as addiction, have been linked to genetic factors (Ducci & Goldman, 2012). In terms of addiction, existing genes of interest are being examined to determine whether they increase susceptibility and vulnerability or increase resilience toward developing a dependency upon chemical substances. This begs the question of whether addiction is inheritable, and if so, what portions of the genome can be manipulated to reduce adverse effects of drug consumption. According to Goldman et al, scientific understanding of addiction is largely enhanced by the identification of genes that play a role in altering substance-specific vulnerabilities and reactions

(2005). This accounts for a variation in drug metabolism or drug receptors and influences the variation in reward or stress resiliency. Adopting a genetics perspective in examining drug use and substance abuse research has caused researchers to focus on the transmission and linkage of specific genes and the neurological basis of addiction. In addition, it has also shed light on evolutionary genetics and the growing field of epigenetics and gene and environment interactions. Recently, the emergence of newer and more accessible software and technology has facilitated access to genetic data which, when paired with behavioral surveys, provides increased potential for the treatment of addiction by understanding and manipulating the genome. Although they possess ethical implications, technologies such as CRISPR-Cas9 provide a promising concept for novel addiction treatment or prevention measures, if there is a potential significant linkage between gene functions and drug action (Li et al., 2020).

Rationale for a Scoping Review

Understanding that the topic of substance use spans multiple disciplines, it is essential to the field to discuss the implications and applications of such research from diverse perspectives. This study aims to synthesize the current knowledge on these major behavioral outcomes of drug use (nicotine dependency, alcoholism, cannabis use, and opioid misuse) as well as other emerging psychoactive substances and behaviors in the field. The aim of this work is to address this lack of synthesis of these studies, providing a specific and relevant body of work and analysis that specifically examines drug addiction in the United States at the intersection of behavioral and biological disciplines. This project will map the extent and range of the existing literature, while also acknowledging the knowledge gaps, common limitations of the current

publications, and the sample composition of the articles that are published in the field and deemed relevant by specific inclusion criteria. Thus, it will produce a thorough analysis of reports studying the intersection of drug abuse, behavior, and health outcomes as it relates to chemical dependency and its related consequences in the United States population.

The Journal on Drug and Alcohol Dependence

The rationale for utilizing this journal for this review is related to the aims of this scoping review aligning with the aims of the editors of the journal *Drug and Alcohol Dependence*. The *j*ournal *Drug and Alcohol Dependence* is an international journal dedicated to publishing research articles, scholarly texts, and commentaries that primarily focus on drug, alcohol, and tobacco use and dependency. The studies featured in the journal range broadly from the genetic and molecular basis of such drug use, the pharmacological influences and actions of the drugs, the associated behavioral outcomes, and human-subject based studies involving treatment and interventions. Such studies utilize methods that span multiple disciplines and fields ranging from biology, sociology, and epidemiology to neuroscience and pharmacology.

The aims of the journal *Drug and Alcohol Dependence* include providing researchers, physicians, and policy makers with access to the scientific literature from different backgrounds and perspectives by consolidating this material into one single journal. It is intended to be an inclusive, accessible resource providing such information after publications selected to be featured have been subjected to rigorous review by editors. The journal *Drug and Alcohol Dependence* editors recognize that drug, alcohol, and tobacco dependence must be studied from an interdisciplinary perspective to increase understanding of substance use and its impact on the

population. The goal is to promote understanding of the multiple aspects that contribute to drug abuse in humans and collect transferable findings that can be utilized to inform drug policy, further scientific studies, expand treatment and prevention practices, and promote successful interventions.

Behavioral and Health Outcomes

In relation to drug abuse and SUD, the behavioral outcomes that are commonly associated include the symptoms and physical results of the pharmacological and chemical interactions occurring between the body and the drug. In this study, there is a special interest in the behaviors that are indicative of dependency and addiction to commonly accessible drugs. Dependency refers to the chronic, progressive impairment - involving psychological, social, and physiological dysfunction - directly associated with psychoactive substance use (Miyasato, 2010). Addiction is characterized by chronic drug seeking despite adverse consequences. Such outcomes of consistent drug use contribute to the stress, decision-making, reward circuitry, and self-control behaviors. The prevalent behavioral outcomes associated in studies of interest can be categorized into the following: tobacco use and nicotine dependency, alcohol use disorder and alcohol consumption, cannabis use, opioid misuse and abuse, and illicit drug use.

Those exhibiting drug abuse behaviors or addiction often experience at least one associated health issue. Health outcomes, such as cancer or lung disease, due to carcinogen exposure of repetitive drug inhalation are prevalent. Pharmacological interaction with drug receptors and chemical changes to brain function are also associated with the dysfunction of neural circuitry, leading to cognitive and psychological disorders. While an individual may be

diagnosed with both SUD and mental disorders, there is insufficient evidence to support the hypothesis that one is caused by the other. In addition, there is a broad and extensive list of factors contributing to an individual's susceptibility to both drug abuse behaviors and psychiatric disorders as they share common risk factors.

In the available studies for review, common comorbidities include lung disease and cancer, psychiatric conditions and disorders, social or cognitive impairment and dysfunction, and death, among others. In addition, the impact of drugs on behavior (decision-making and risk-reward behaviors) has also linked drug use to infectious disease susceptibility. Sharing drug injection equipment and an increase in risk-taking or reckless behavior often contributes to drug use associations with hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

Honor's Project in Biobehavioral Health

The proposed project addresses the three dimensions of scholarship of the Department of Biobehavioral Health at The Pennsylvania State University. These dimensions are biological, behavioral and health. It addresses the topic of substance abuse from a transdisciplinary perspective. The biological dimension is addressed through a focus on the genotypes associated with substance use. This is clearly delineated in the inclusion/exclusion criteria for the studies being analyzed. The behavioral dimension is addressed by: 1) focusing on substance use as a focal area, 2) documenting different behaviors captured under the broad umbrella of substance use, or 3) focusing on those with substance use as the target study population. This is accomplished in three ways: 1) the selection of a research outlet that focuses on substance use (*Drug and Alcohol Dependence*), 2) focusing on substance abuse as an outcome, and/or 3)

substance use being a condition of the sample being analyzed within the study. Finally, the project addresses health by including information on health outcomes studied as part of the articles included in the analysis, with commonly associated health outcomes ranging from mental health status to physical consequences and comorbidities. Aside from covering each individual dimension of Biobehavioral Health, this thesis will provide a synthesis of the body of literature and highlight specific elements of study design such as target population, sample composition, and inclusion of limitations.

Chapter 2

Methods

In order to fully examine the association between genes of interest, drug and alcohol use behaviors, and related health outcomes that is currently publicly available, it was determined that a scoping review would be beneficial. Utilizing a scoping review as the approach allows for the researcher to outline the current knowledge and understanding while also identifying the potential gaps of knowledge that remain in the literature (Arksey & O'Malley, 2005). This scoping review was conducted in accordance with the steps outlined by Arksey & O'Malley (2005): identifying the question or purpose of the research effort, identifying relevant studies for further analysis, selecting the studies, collecting and organizing the data, and summarizing and reporting the results. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for Scoping Reviews checklist was also utilized to provide guidance for synthesizing the key concepts and relevant findings (Tricco et al., 2018).

Peer-reviewed literature deemed relevant for the study was obtained through a utilization of the ScienceDirect platform. This study included all articles published in the journal *Drug and Alcohol Dependence*, which is one of the flagship journals in the area of interest. Access to ScienceDirect and the journal *Drug and Alcohol Dependence* were provided by The Pennsylvania State University. The database was searched using the term of interest ("*genotype*"). Studies included in the analysis were those published between the years of 2000-2023. We excluded those which were not categorized as a "Research Article" as determined by the journal's publication criteria, resulting in 226 research articles available for analysis. Additionally, articles were excluded if they were not conducted in the United States or primarily

discussed a population outside of the United States and did not discuss a specific gene or genotype, further excluding another 93 articles. Despite not being the focal point of the analysis, comments are provided (when needed) to highlight instances of interest within the excluded articles. The remaining 133 articles obtained were analyzed. A clear flowchart for the articles being considered is shown in Figure 1 in Chapter 3. From each article, the following data were extracted and organized in a database: Article Title; Year of Publication; Genes or Genotypes of interest; Behavioral outcomes studied; Sample size; Stage of lifespan of the population; Health outcomes discussed; and Study limitations (whether or not they existed, and qualitative information).

Each article is given a unique ID for purposes of being identified across our summary tables or within the text. In Appendix Table A (Table A, hereafter), the following data are presented: Article ID; Article - Authors and Title; Year of Publication; and Genes or Genotypes of interest. For purposes of simplicity, we omit the article names and authors from any subsequent tables. However, the Article ID is included in each table to allow the reader to consult when needed. In Appendix Table B (Table B, hereafter), the following data are presented: Article ID; Behavioral outcomes studied; and Health outcomes discussed. In Appendix Table C (Table C, hereafter) the following data are presented: Stage of lifespan of the population; Sample size; Study limitations (whether or not they existed, and qualitative information). In summary, Tables A and B show information about the biobehavioral aspect of each study and Table C presents information about study design elements.

All data were analyzed using Statistical Package for the Social Sciences, commonly known as SPSS. This software was accessed through the Pattee and Paterno Library at The

Pennsylvania State University. All data retrieval, processing instructions, and analytic data necessary to replicate this study are included as part of this document.

Chapter 3

Results

First, I accessed the journal *Drug and Alcohol Dependence* through *ScienceDirect*. With the browse tool, I was provided access to all studies published between 2000 and 2023. Search results (n = 10,993) were filtered to determine whether they met the pre-screening inclusion criteria described in the Methods section. The first exception were those articles that did not meet the inclusion criteria of being a research article (n = 133) or referencing a specific genotype (n = 10,634). Articles that met the initial inclusion criteria (n = 226) were then downloaded from Elsevier and saved to the device. After obtaining these articles in bulk, they were screened to determine whether they adhered to further exclusion criteria. Studies conducted outside of the United States (Australia, Asia, Europe, etc.) were excluded (n = 93). These excluded articles were recorded in a Microsoft Excel sheet independent of those being screened and analyzed for the project. This allowed us to reach our sample of 133 articles. Upon further review, we found articles that were downloaded but did not fit specific criteria, leading to additional exclusions. Research articles that did not specify a gene of interest, or associated gene for the behavioral outcome or health outcome of interest were excluded (n = 13). The remaining studies (n = 120) constitute the analytic sample for the thesis. These articles were thoroughly analyzed for review and information extracted from these studies was organized utilizing the spreadsheet to facilitate the analysis.

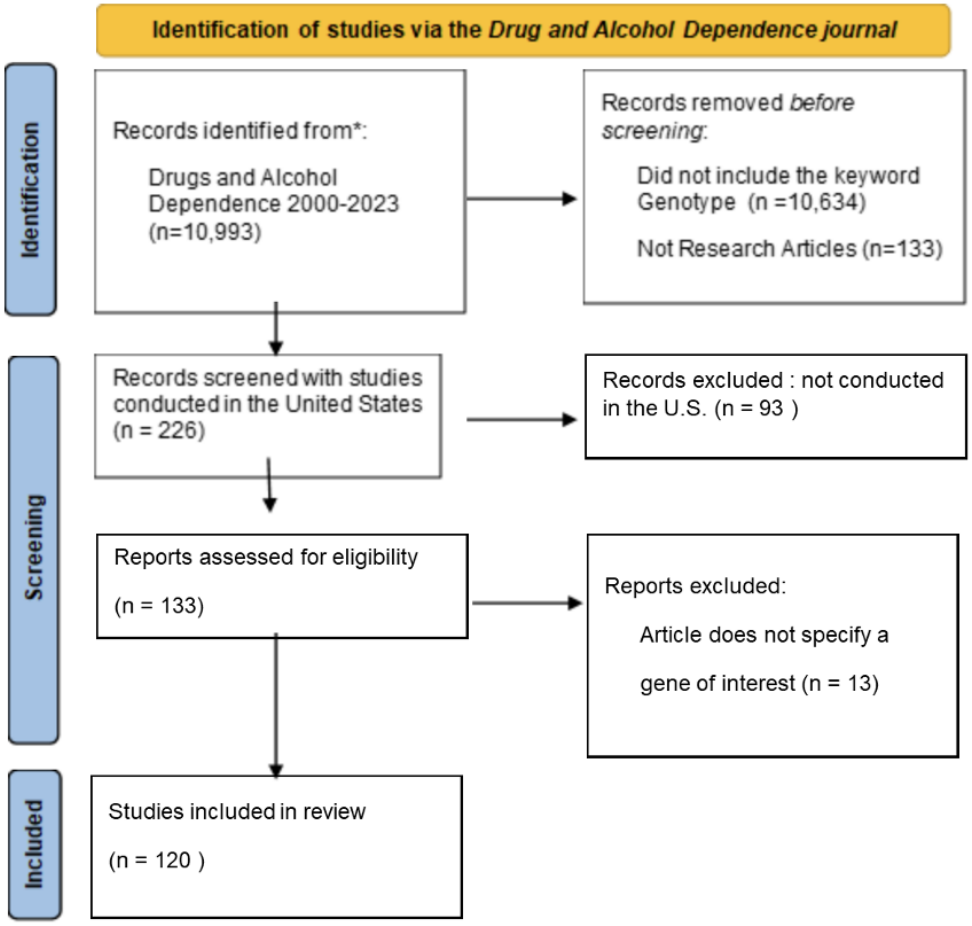

Figure 1. PRISMA Flowchart and Identification and Screening of Relevant Articles in the journal Drug and Alcohol Dependence. Studies must meet the following inclusion criteria: (1) publication year between 2000-2023, (2) all populations studied, and experiments conducted, are within the United States, and (3) the article must identify a gene or genotype of interest.

Total Articles by Publication Year

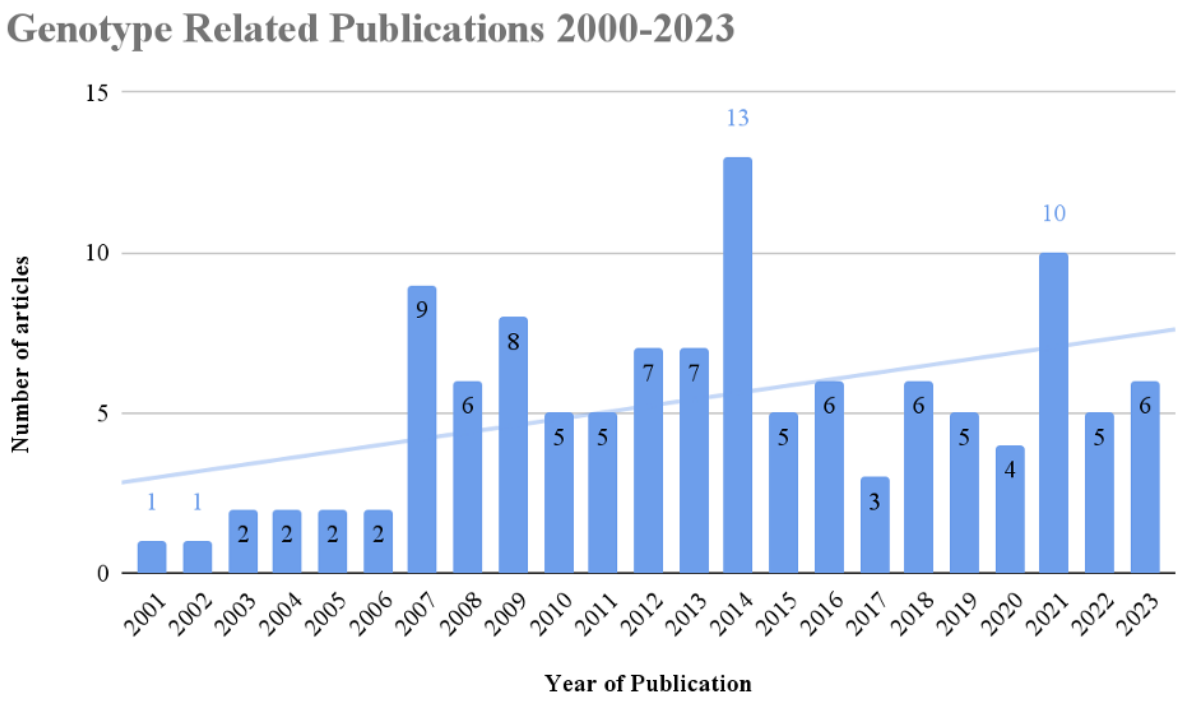

Figure 2. Trends in Genotypic Studies Published in the Journal on Drug and Alcohol Dependence. Results from utilizing the search term "*genotype*" in the journal of Drug and Alcohol Dependence meeting inclusion criteria were categorized by year of article publication.

At the beginning of the century, articles centering the intersection of drug and alcohol consumption and genetics that met the criteria outlined for this review were low. From 2000 to 2002, there was only one article per year fitting the aforementioned criteria. However, there was a slight increase from 2003 to 2006, with two research articles per year being published in the journal that fit the criteria. This was followed by a dramatic increase in 2007 to nine articles. This increase coincides with the final years of the first wave of the Prescription Opioid Epidemic. There was a slight decrease in 2008 with only six relevant articles being published,

before another increase similar to 2007 when eight relevant articles were published in 2009. Following this, there remained a consistent annual output of five to seven relevant publications from the journal until 2014, when a peak of 13 articles was reached. As seen in Figure 2, the highest number of research articles per year was published in 2014. Following this, there is a decrease in publications observed, with a consistent output of three to six relevant articles published each year, from 2015 to 2020. There was an increase in the publication of relevant articles in 2021, with the number of articles being 10. Following this, in more recent years (2022 to 2023), there was an output of 5-6 relevant articles per year being selected for publication in the journal. Since the first major increase in 2007, the number of published articles remains about four per year.

Sample Size

Historically, genetic studies have had small sample sizes. The studies that met the inclusion criteria for this review also reflected this. Only one study, an outlier, had more than 10,000 observations and this is because it included data from multiple studies. Thus, the sample size average is biased by this large value. While the range of sample sizes was from 8 to 1,936,764 individuals or subjects, the majority of the values are in the lower range of the distribution. This can be seen in Figure 3, below.

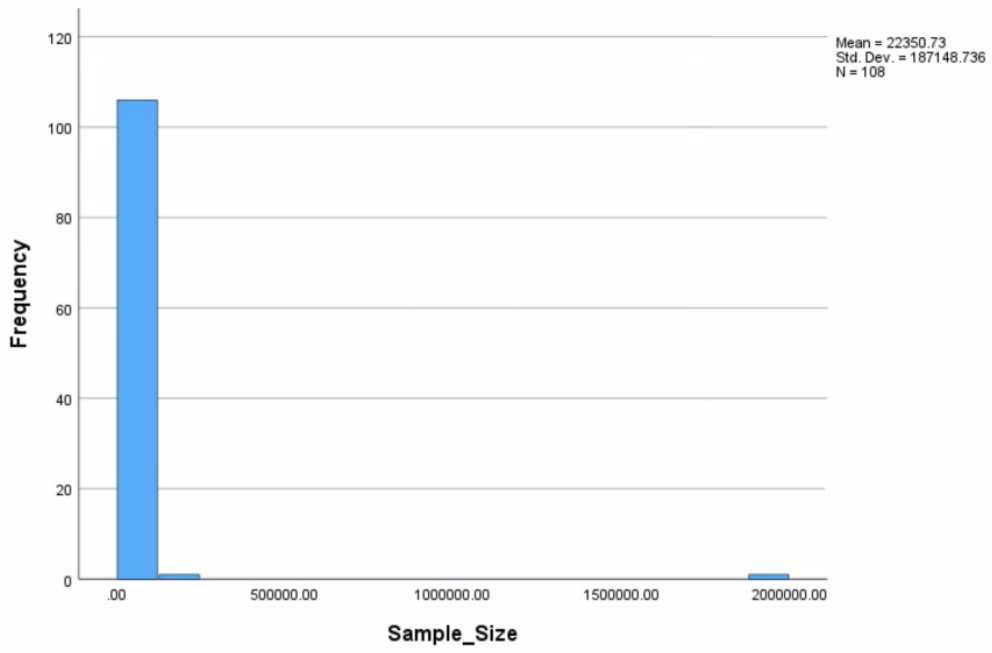

Figure 3. Histogram of the Sample Size Distribution of Studies Analyzed from the Journal on Drug and Alcohol Dependence. Sample sizes observed from articles included range from n=8 to n=1,936,764 with the majority of the sample sizes falling on the left side of the distribution.

Sample Demographics

Out of the 120 studies included in this scoping review, 14.17% concentrated on adolescent sample populations and 70.83% described their sample as adults. 78 (65%) of the total articles explicitly stated the mean age of participants or human subjects. After excluding animal model information and not accounting for vague ranges of sample age (n=52), the mean age of the samples in the reviewed articles was 34.07 (± 13.75) years. Average sample ages ranged from 9.91 years of age to 75.5 years of age. Additionally, a majority of these studies described their sample population as non-Hispanic Caucasian or those of European descent, with

the remaining study populations as follows: 11.67% African American and 6.67% Hispanic or Latino/a/x. It is essential to also note that a majority of the studies involved non-diverse samples. This has been identified as a limitation of the field of biodemography, behavioral genetics, and genetics in general - mapping on to subspecialities such as behavioral genetics and substance use (as documented here). In conclusion, it seems the limitation(s) of the general field is/are applicable to studies that concentrate on substance use.

Recognition of Limitations of Analyzed Studies

A total of 116 (96.67%) of the 120 analyzed studies from the journal *Drug and Alcohol Dependence* explicitly addressed the limitations that impacted the results or conclusions drawn from their studies. This is a high percent and reveals the fact that researchers, and the journal, are cognizant of the limitations of the research. Of these reports, the majority noted five major limitations: 1) sample size or demographics was restrictive in terms of making generalizations, 2) self-report bias or response bias present, 3) confounding variables, factors, or underlying genetic or health influence, 4) misclassification or misdiagnosis due to novel or subjective diagnostic tests, and 5) data were obtained via a large database or previously collected genetic database, as opposed to a study-specific sample.

The first limitation is in line with what was discussed in the Sample Demographics section before. Self-reports are present, but they likely stem from possible recall or reporting bias which is present in any study that involves a survey or questionnaire component. The limitation on confounding covariates, also related to what data are collected or available, is worth noting as it is possible some of the associations may be underestimated/overestimated due to model

specification. The fourth limitation is possible as we have observed major developments in health technology over the past 23 years. As such, diagnoses have become better. However, this limitation is still a concern, particularly as it relates to studying populations of interest (people with a specific condition) or when issues of underdiagnoses are present. The final limitation is a staple of the field as it is common for researchers to collect data and aggregate it to make more analyses possible. Further information regarding specific study limitations and confounds is available in Table C.

Genetic Influences and Genotypes of Interest

Specific genotypes of interest or genes discussed were recorded during data collection to determine the prevalence of certain genotypes within this body of research. The 120 reports analyzed included a total of 87 unique genes, proteins, receptors, viruses, and cell types chosen as the biological marker of interest. The top 15 categories are available in Table 1, with the remaining genes, proteins, viruses, and cell types available in Appendix Table A. The percentage displayed refers to the proportion of articles focused on each genotype of interest. I must note that the frequency presented in the table is higher than the number of articles included in the review. This is due to some articles studying more than one gene or genetic marker of interest.

Table 1. Categorical Distribution of Genes and Biomarkers. The 15 categories of genes or biomarker groups with the highest frequency of mention are listed in descending order.

Gene of Interest	Frequency	Percentage
chromosome loci	32	26.67%
OPRM1 (and associated mu-opioid receptor and variants)	19	15.83%
Dopamine receptors/neurotransmitters (DRD2/DRD4/DAT1)	19	15.83%
HCV	16	13.33%
cytochrome P450 family (CYP2A6/CYP2B6)	11	9.17%
CHRNA4- CHRNA5- CHRNA6	11	9.17%
various single nucleotide polymorphisms (SNPs)	9	7.50%
5-HTT (serotonin transporter); SLC64A	6	5%
genome-wide association studies	7	6%
Taq1A SNP	5	4.17%
GABRA2	4	3.33%
alcohol dehydrogenase (ADH) gene cluster	4	3.33%
CD4 T-cells	3	2.50%
GABA(A)/ GABA(B)	3	2.50%
MAO-A/MAO-B	3	2.50%

Note: For additional information, see Appendix Table A.

Behavioral Outcomes

Studies published in the journal *Drug and Alcohol Dependence* focus on behavioral outcomes and interventions related to reward-circuitry behaviors and substance abuse disorders. Notable behavioral outcomes studied in the articles included in the analysis can be divided into the following categories: alcohol dependency and alcohol consumption (35.83%); nicotine dependency (20.0%); opioid dependency, including morphine and heroin (12.5%); general substance use disorder (10.83%); marijuana and cannabis use (11.67%); injection drug use, including methamphetamine (5.83%); cocaine use (5.83%); and other various outcomes, including toluene and oxycodone use (3.33%). In addition, a number of the studies reviewed (13.33%) primarily discussed two of the aforementioned categories, and two of the 120 reviewed articles simultaneously discussed three behavioral outcomes. Further information regarding these categories is available in Appendix Table B.

Health-related Outcomes

Furthermore, 71 (59.16%) of the articles analyzed discussed a broad range of associated health outcomes, with many of these studies examining multiple disorders and outcomes spanning different categories simultaneously. The specific breakdown from each category is as follows: 31.17% discussed psychiatric disorders (major depressive disorder, dysphoria, and mood disorders; schizophrenia and drug-induced paranoia; attention-deficit/hyperactivity disorder (ADHD); post-traumatic stress disorder (PTSD); and anxiety disorders), 16.67% mentioned social and academic problems (conduct disorder, deviance, or impulsivity; and

cognitive dysfunction and locomotor or memory impairment), 15.0% discussed viral infections (human immunodeficiency virus (HIV) and hepatitis C virus (HCV)), 5.0% mentioned chronic pain, and 5.0% discussed cirrhosis or liver disease. Less than 5.0% of the articles featured discussion of the following health outcomes: chronic stress, cancer (lung or liver), childhood maltreatment, adverse pregnancy outcomes (including neonatal abstinence syndrome), death, and insomnia. The remaining articles (40.83%) lack mention of a health outcome associated with the behavioral outcome or gene of interest. These health outcome categories and additional information regarding their associated behavioral outcomes are also available in Appendix Table B. Further, more information for each study included in this thesis is available in the Appendix Tables.

Chapter 4

Discussion

This thesis sought to explore the scholarship on genetics in the journal *Drug and Alcohol Dependence*, one of the main journals in the field. Based on the study protocol and the data analysis, conducted as part of this scoping review, it is difficult to confirm whether an association between substance abuse, genetics, behavior, and health outcomes is explicitly and actively being studied within the field. Approximately 2% of the articles or 226 articles were explicitly on this topic, but only about 1% or 120 articles were conducted in the United States. As documented, some studies focused on non-human subjects, reducing the already limited number of studies. There were major discrepancies and variations in study design, sample demographics, and genetic, behavioral, and health outcomes. Of the 120 articles deemed eligible for analysis based on the aforementioned inclusion criteria, about 59.16% mentioned related health outcomes and there was a significantly broad range of behavioral outcomes and genotypes discussed. The behavioral outcomes of interest were disproportionately studied, with an emphasis on alcohol consumption, nicotine use, and opioid misuse. However, this likely aligns with the drug overdose and morbidity trends in the United States at the time of publication. Simply said, as the dynamics of substance use change, so do the areas of interest.

Furthermore, the peaks in publication years evident in Figure 2 demonstrate the trends of research focusing on behavioral and health outcomes in the United States - with some form of genetic or genotypic focus. For example, the highest peak of articles published in 2014 aligns with reports of an increase to 10.2% of Americans of at least 12 years of age using illicit drugs, compared to percentages reported within the study period (SAMHSA, 2015). In addition, the

second highest peak of articles published in 2021 follows rising interest in the topic due to the opioid epidemic and the peak of the COVID-19 pandemic in 2020, when there was a 23% increase in alcohol abuse and 16% increase in drug abuse in the United States (Chacon et al., 2021). Lastly, the publication year of 2007 is the third highest peak in publications. According to the Centers for Disease Control and Prevention (CDC), 20% of adolescents and 90% of adults reported the use of prescription drugs in the past month in surveys conducted in 2007-2008 (Gu et al., 2010). Thus, the publication trends of articles being produced on the topic in any given year, as well as the content and study design, are representative of the public health trends regarding substance use outcomes in the nation.

The studies currently available for review examine a broad range of genotypes associated with substance abuse (see the Results section). However, the distribution of the frequency genotype occurrence in the articles clearly favored about a dozen genes. Table 1 shows the 15 most studied genes and genotypes in the journal from 2000-2023 while examining a US-based sample. This accounts for a majority of the 120 articles, suggesting a potential oversaturation of publications featuring the same genotypic foci, instead of examining novel genes within the population. Nevertheless, as mentioned before, there is variation within these studies.

The top three topics of interest reveal an interesting pattern. Studies concerning chromosome loci account for approximately one-fourth of article topics. Chromosome loci are regions on a chromosome that code for a gene, with loci on chromosomes 4, 5, 9-11, and 17 being previously linked to predisposition or susceptibility to multiple substances (Li & Burmeister, 2009). Relating to opioid misuse and the opioid epidemic, OPRM1, which codes for the mu-opioid receptor, allows opioid drugs to bind and perform their pharmacological action (Taqi et al., 2019). These receptor genes account for almost 16% of articles, the second highest

frequency observed. Lastly, dopamine receptors and neurotransmitters (DRD2, DRD4, and DAT1) are the third highest in terms of study frequency. These genes are generally associated with nicotine and alcohol abuse but have also been linked to attention deficit/hyperactivity disorder (ADHD) (Blum et al., 2008). This is likely due to dopamine's association in the mesolimbic system (including the ventral tegmental area, striatum, amygdala, prefrontal cortex, and hippocampus) and its role in mediating reward and motivation (Lewis et al., 2021). These three genes, alone, account for the majority of examined genotypes of interest, with a combined frequency of 70/120. While the 120 studies consider an abundance of genes, the aforementioned distribution of genes in Table 1 implies that there are genotypes that have been neglected in the field, such as SOCS-3 and UTP20 among others, as they were examined in <1% of studies included in the review. All genes of interest observed are listed in Table A.

Although a growing topic of interest in the field, the lack of research on adolescent drug use and health and behavioral outcomes demonstrates a gap in knowledge in the literature. Only 14.17% of articles expressed an interest in studying an adolescent and teenager (<18 years of age) sample. Further, the majority of articles published in the years 2000-2023 have included study samples with the average age of 34.07 years, revealing a strong emphasis on adult behavioral and health outcomes regarding substance use. However, according to the Centers for Disease Control and Prevention (CDC), the majority of adults meeting the criteria for substance use disorder started their substance use behavior in their teen years (CDC, 2022). This underscores the need to focus on this stage of the life course. A significant proportion of available literature that can be generalized to the American population examines current adult behaviors and long-term effects of substance abuse, overlooking the potential role of adolescent

development and childhood behaviors and treatment on the prevention and manifestation of substance abuse behaviors.

Another gap in knowledge is the lack of research that can be generalized and applied, specifically to racial and ethnic groups besides those described as of "European descent" or "Caucasians", ways to describe the non-Hispanic white population. African American populations have the highest percentage of rare single nucleotide polymorphisms SNPs and members of the Hispanic and Latino/a/x communities also possess admixed genomes, possessing a genetic ancestry that spans multiple regions and racial groups (Campbell & Tishkoff, 2010; Conomos et al., 2016). Despite the average sample size being moderate (relatively small), the current review was only able to identify African American and Hispanic or Latino/a/x representation in the sample groups of 11.67% and 6.67% of the articles, respectively. In the limitations of a broad majority of studies, there is a mention of intentional exclusion of "non-Caucasian groups' ' to prevent genetic confounds. The exclusion of these groups and lack of contextualization about the applicability of results from most studies with these groups as the focus sample generates a collection of research findings that are only generalizable to a subset of the US population.

While not thoroughly analyzed, excluded articles included more associated genetic, behavioral, and health outcomes than those fitting the criteria for analysis. It is worth noting that the articles not included in this review due to study site, location, or sample nationality did demonstrate a well-rounded collection of articles concerned with the genetic, behavioral, and health components of substance abuse worldwide. The use of "genotype" as a search term seems to have yielded many articles that focused on broad studies regarding genetic studies without explicitly providing background or mention of a specific gene or genotype, thus excluding an

additional 92 articles. These excluded publications provide insight into genetic linkages to substance abuse. Nevertheless, the genetic diversity present in the United States and the behavioral and health habits and outcomes present in the American population differ from other regions of the world. So does the way society deals with such issues (e.g., treatment vs. punitive measures, access to care). Thus, it was essential to limit studies to the population of interest and specific genotypes that have been linked to these outcomes.

A limitation of this scoping review was that the quality of the study and its design were not analyzed. However, this is acknowledged in the decision to include only the peer-reviewed research articles available through the journal on *Drug and Alcohol Dependence*. Given these articles are published in one of the major journals in the field, it is assumed that the peer-reviewed process filtered studies of lower quality or that required revisions. While the peer-reviewed system has its flaws, it continues to be the gold-standard in recognizing work quality. Problematic papers would have been retracted. Additionally, this review does not include current literature about the genetic, behavior, and health components of substance abuse that were published outside of the journal on *Drug and Alcohol Dependence*, but this was how the thesis project was designed. Finally, the use of the search term "*genotype*" as the single term utilized to identify articles likely limited the search results and, thus, the articles included in the review. Alternative searches with terms like "polygenic risk score" and "genetics" yielded a similar number of initial articles (less than 3%), yielding validity to my research approach. In conclusion, the studies encompass a broad range of genotypes (SNPs, chromosome loci, dopamine transporter genes, and mu-opioid receptor genes) and their association with specific behavioral outcomes (e.g., nicotine dependency, alcohol dependency, opioid misuse). However, they do not connect these associations to the physical manifestations and health outcomes that

affect the United States population, as a vast number of these studies do not mention any health outcome. This is an area of growth for the field. Regarding study design and limitations, although average sample size is not a limitation for some of the studies, generalizations and suggestions of causal effects cannot be presented due to the prevalent exclusion of ethnic and racial groups, besides for non-Hispanic white populations (described as “European-Americans” and/or “Caucasians”). In addition, the omission of adolescents in study samples limits findings to long-term outcomes in adulthood and results do not account for the effect of childhood adversity and developmental factors. The results of this scoping review highlight a need for new studies to include more genetically diverse participants or subjects. To fully address the public health concern of substance use and its associated comorbidities in the United States, and develop new treatments and preventative interventions, it is essential that it is observed from multiple scientific perspectives and disciplines. The results presented in this project highlight numerous ways in which the field can grow to address the need for more research and to make this research more inclusive in terms of topics, focal areas, and study population.

Appendix A: Article Identification and Genes of Interest

ID	Publication Year	Article Title & Author(s)	# of Genes	Gene_1	Gene_2	Gene_3	Gene_4	Gene_5	Gene_6
1	2001	Early clinical manifestations of cannabis dependence in a community sample. Rosenburg, MF., Anthony, JC.	1	ANKFN1 gene					
2	2002	Treating hepatitis C in methadone maintenance patients: an interim analysis. Sylvestre, DL	1	HCV					
3	2003	Effects of heroin and its metabolites on schedule-controlled responding and thermal nociception in rhesus monkeys: sensitivity to antagonism by quadazocine, naltrindole and ß-funaltrexamine. Negus, S. S., Brandt, M. R., Gatch, M. B., & Mello, N. K.	1	mu opioid receptors					
4	2003	A genome-wide search for quantitative trait loci influencing substance dependence vulnerability in adolescence. Stallings, M. C., Corley, R. P., Hewitt, J. K., Krauter, K. S., Lessem, J. M., Mikulich, S. K., ... & Crowley, T. J	5	locus on chromosome 3q24-25	locus on chromosome 9p34	locus on chromosome 11p15	locus on chromosome 20q11	locus on chromosome 20p11	
5	2004	A comparison of HCV antibody testing in drug-free and methadone maintenance	1	HCV					

		treatment programs in the United States. Strauss, S. M., Astone, J. M., Des Jarlais, D., & Hagan, H.							
6	2004	The utility of indirect predictors of hepatitis C viremia. Sylvestre, D. L., & Clements, B. J.	1	HCV					
7	2005	Genetic influences on quantity of alcohol consumed by adolescents and young adults. Hopfer, C. J., Timberlake, D., Haberstick, B., Lessem, J. M., Ehringer, M. A., Smolen, A., & Hewitt, J. K.	3	DRD2 & DRD4	5-HTT; SLC64A	Taq1A SNP			
8	2005	DRD2 genotypes and substance use in adolescent children of alcoholics. Conner, B. T., Noble, E. P., Berman, S. M., Ozkaragoz, T., Ritchie, T., Antolin, T., & Sheen, C.	1	DRDR A1 allele (A1A1/A1A2 genotypes) or the A1 allele (A2A2 genotype)					
9	2006	Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. Kalayasiri, R., Kranzler, H. R., Weiss, R., Brady, K., Gueorguieva, R., Panhuysen, C., ... & Malison, R. T.	1	dopamine transporter, dopamine β-hydroxylase					
10	2006	Association of a D2S2944 allele with depression specifically among those with substance abuse or antisocial personality. Langbehn, D. R., Philibert, R., Caspers, K. M., Yucuis, R., & Cadoret, R. J.	1	D2S2944 allele					

11	2007	Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. Budney, A. J., Vandrey, R. G., Hughes, J. R., Moore, B. A., & Bahrenburg, B.	1	CNR1					
12	2007	Deriving phenotypes for molecular genetic studies of substance use disorders: A family study approach. Faraone, S. V., Adamson, J. J., Wilens, T. E., Monuteaux, M. C., & Biederman, J.	1	CDH13					
13	2007	Test of association between TaqIA A1 allele and alcohol use disorder phenotypes in a sample of adolescent patients with serious substance and behavioral problems. Sakai, J. T., Hopfer, C. J., Hartman, C., Haberstick, B. C., Smolen, A., Corley, R. P., ... & Crowley, T. J.	1	Taq1A A1 allele					
14	2007	Evidence for specificity of transmission of alcohol and nicotine dependence in an offspring of twins design. Volk, H. E., Scherrer, J. F., Bucholz, K. K., Todorov, A., Heath, A. C., Jacob, T., & True, W. R.	2	CYP1A1	GSTT1				
15	2007	Test of association between TaqIA A1 allele and alcohol use disorder phenotypes in a sample	1	Taq1A A1 allele					

		of adolescent patients with serious substance and behavioral problem. Sakai, J. T., Hopfer, C. J., Hartman, C., Haberstick, B. C., Smolen, A., Corley, R. P., ... & Crowley, T. J.							
16	2007	A genome-wide scan for loci influencing adolescent cannabis dependence symptoms: Evidence for linkage on chromosomes 3 and 9. Hopfer, C. J., Lessem, J. M., Hartman, C. A., Stallings, M. C., Cherny, S. S., Corley, R. P., ... & Crowley, T. J.	2	locus on chromosome 3q21	locus on chromosome 9q34				
17	2007	The role of conduct disorder in explaining the comorbidity between alcohol and illicit drug dependence in adolescence. Button, T. M., Rhee, S. H., Hewitt, J. K., Young, S. E., Corley, R. P., & Stallings, M. C.	3	ADH1B	CYP2A6	CHRNA5			
18	2007	Using mathematical modeling and control to develop structured treatment interruption strategies for HIV infection. Rosenberg, E. S., Davidian, M., & Banks, H. T.	1	CD4 T-cells					
19	2007	Evaluation of OPRM1 variants in heroin dependence by family-based association testing and meta-analysis. Glatt, S. J., Bousman, C., Wang, R. S., Murthy, K. K., Rana, B. K., Lasky-Su, J. A., ... & Tsuang, M. T.	1	*OPRM1 variants*					

20	2008	Familial transmission of derived phenotypes for molecular genetic studies of substance use disorders. Faraone, S. V., Adamson, J. J., Wilens, T. E., Monuteaux, M. C., & Biederman, J.	1	D1 and D2 (dopamine) receptors					
21	2008	Genetic variation in the serotonin pathway and smoking cessation with nicotine replacement therapy: New data from the Patch in Practice trial and pooled analyses. David, S. P., Johnstone, E. C., Murphy, M. F., Aveyard, P., Guo, B., Lerman, C., & Munafò, M. R.	3	TPH1 A779C	SLC6A4 5-HTTLPR	HTR1A C-1019G			
22	2008	Racial and ethnic changes in heroin injection in the United States: Implications for the HIV/AIDS epidemic. Broz, D., & Ouellet, L. J.	1	HCV					
23	2008	Genomewide linkage survey of nicotine dependence phenotypes. Sullivan, P. F., Kuo, P. H., Webb, B. T., Neale, M. C., Vittum, J., Furberg, H., ... & Kendler, K. S.	2	chr7 (D7S2252 to D7S691)	chr18 (D18S6)				
24	2008	Association of candidate genes with antisocial drug dependence in adolescents. Corley, R. P., Zeiger, J. S., Crowley, T., Ehringer, M. A., Hewitt, J. K., Hopfer, C. J., ... & Krauter, K.	5	CHRNA2	CNR1	CYP2B6	HTR7	GRIA1	
25	2008		6	chromoso me 1	chromosome 10	chromosome 10	chromosome 2	chromosome 13	chromosome 14

		Linkage scan for quantitative traits identifies new regions of interest for substance dependence in the Collaborative Study on the Genetics of Alcoholism (COGA) sample. Agrawal, A., Hinrichs, A. L., Dunn, G., Bertelsen, S., Dick, D. M., Saccone, S. F., ... & Bierut, L. J.							
26	2009	Genetic correlates of morphine withdrawal in 14 inbred mouse strains Metten, P., Crabbe, J. C., & Belknap, J. K.	1	μ-opioid receptor genes					
27	2009	Perceived peer delinquency and the genetic predisposition for substance dependence vulnerability. Button, T. M., Stallings, M. C., Rhee, S. H., Corley, R. P., Boardman, J. D., & Hewitt, J. K.	1	GABRA2					
28	2009	Morphine-induced physiological and behavioral responses in mice lacking G protein-coupled receptor kinase 6. Raehal, K. M., Schmid, C. L., Medvedev, I. O., Gainetdinov, R. R., Premont, R. T., & Bohn, L. M. (	1	GPCR protein kinase 6					
29	2009	Health-related quality of life in methadone maintenance patients with untreated hepatitis C virus infection. Batki, S. L., Canfield, K. M., Smyth, E., & Ploutz-Snyder, R.	1	HCV					
30	2009	Daily ratings measures of alcohol craving during an	1	OPRM1					

		inpatient stay define subtypes of alcohol addiction that predict subsequent risk for resumption of drinking. Oslin, D. W., Cary, M., Slaymaker, V., Colleran, C., & Blow, F. C.							
31	2009	The association between cannabinoid receptor 1 gene (CNR1) and cannabis dependence symptoms in adolescents and young adults. Hartman, C. A., Hopfer, C. J., Haberstick, B., Rhee, S. H., Crowley, T. J., Corley, R. P., ... & Ehringer, M. A.	1	cannabinoid receptor 1 gene (CNR1)					
32	2009	Acute responses to nicotine and smoking: Implications for prevention and treatment of smoking in lower SES women. Perkins, K. A.	2	DRD2	DRD4				
33	2009	An interaction between DAT1 and having an alcoholic father predicts serious alcohol problems in a sample of males. Vaske, J., Beaver, K. M., Wright, J. P., Boisvert, D., & Schnupp, R.	1	DAT1					
34	2010	EEG spectral phenotypes: Heritability and association with marijuana and alcohol dependence in an American Indian community study. Ehlers, C. L., Phillips, E., Gizer, I. R., Gilder, D. A., & Wilhelmsen, K. C.	1	N/A					
35	2010	Randomized, double-blind, placebo-controlled trial of	1	Val158Met					

		modafinil for the treatment of methamphetamine dependence. Heinzerling, K. G., Swanson, A. N., Kim, S., Cederblom, L., Moe, A., Ling, W., & Shoptaw, S.		polymorphism in the catechol-O-methyltransferase gene					
36	2010	Abuse liability of oxycodone as a function of pain and drug use history. Comer, S. D., Sullivan, M. A., Vosburg, S. K., Kowalczyk, W. J., & Houser, J.	1	CYP2D6					
37	2010	Alcohol impairs interferon signaling and enhances full cycle hepatitis C virus JFH-1 infection of human hepatocytes. Ye, L., Wang, S., Wang, X., Zhou, Y., Li, J., Persidsky, Y., & Ho, W.	4	HCV	IFN regulatory factors (IRF-5 and IRF-7)	STAT-1 and STAT-2	SOCS-3		
38	2010	Test of association between GABRA2 (SNP rs279871) and adolescent conduct/alcohol use disorders utilizing a sample of clinic referred youth with serious substance and conduct problems, controls and available first-degree relatives. Sakai, J. T., Stallings, M. C., Crowley, T. J., Gelhorn, H. L., McQueen, M. B., & Ehringer, M. A.	1	GABRA2 (SNP rs279871)					
39	2011	Linkage scan of alcohol dependence in the UCSF Family Alcoholism Study. Gizer, I. R., Ehlers, C. L., Vieten, C., Seaton-Smith, K. L.,	2	chromosome 4q containing the alcohol	chromosome 4p that contains a GABAA receptor				

		Feiler, H. S., Lee, J. V., ... & Wilhelmsen, K. C.		dehydrogenase (ADH) gene cluster	subunit gene cluster				
40	2011	Genetic moderators and psychiatric mediators of the link between sexual abuse and alcohol dependence. Copeland, W. E., Magnusson, Å., Göransson, M., & Heilig, M. A.	3	CRHR1	MAO-A	OPRM1			
41	2011	Strategies for characterizing complex phenotypes and environments: General and specific family environmental predictors of young adult tobacco dependence, alcohol use disorder, and co-occurring problems. Bailey, J. A., Hill, K. G., Meacham, M. C., Young, S. E., & Hawkins, J. D.	1	GABRA2					
42	2011	Chronic hepatitis C virus infection and increases in viral load in a prospective cohort of young, HIV-uninfected injection drug users. Boodram, B., Hershow, R. C., Cotler, S. J., & Ouellet, L. J.	1	HCV infection					
43	2011	Associations among types of impulsivity, substance use problems and Neurexin-3 polymorphisms. Stoltenberg, S. F., Lehmann, M. K., Christ, C. C., Hersrud, S. L., & Davies, G. E.	3	NRXN1 (2p16.3)	NRXN2 (11q13)	NRXN3 (14q31)			

44	2012	Nicotine dependence and comorbid psychiatric disorders: Examination of specific genetic variants in the CHRNA5-A3-B4 nicotinic receptor genes. Chen, L. S., Xian, H., Grucza, R. A., Saccone, N. L., Wang, J. C., Johnson, E. O., ... & Bierut, L. J.	1	CHRNA5 -A3-B4 nicotinic receptor genes					
45	2012	ANAPC1 and SLCO3A1 are associated with nicotine dependence: Meta-analysis of genome-wide association studies. Wang, K. S., Liu, X., Zhang, Q., & Zeng, M.	2	ANAPC1	SLCO3A1				
46	2012	Association between CHRNA5 genetic variation at rs16969968 and brain reactivity to smoking images in nicotine dependent women. Janes, A. C., Smoller, J. W., David, S. P., Frederick, B. D., Haddad, S., Basu, A., ... & Kaufman, M. J.	1	CHRNA5 (rs169699 68)					
47	2012	Different genes influence toluene- and ethanol-induced locomotor impairment in C. elegans. Davies, A. G., Friedberg, R. I., Gupta, H., Chan, C. L., Shelton, K. L., & Bettinger, J. C	4	slo-1	rab-3	unc-64	unc-79		
48	2012	Does the “gateway” sequence increase prediction of cannabis use disorder development beyond deviant socialization? Implications for prevention practice and policy.	1	MAOA gene					

		Tarter, R. E., Kirisci, L., Mezzich, A., Ridenour, T., Fishbein, D., Horner, M., ... & Vanyukov, M. (2012).							
49	2012	Childhood adversity, serotonin transporter (5-HTTLPR) genotype, and risk for cigarette smoking and nicotine dependence in alcohol dependent adults. Mingione, C. J., Heffner, J. L., Blom, T. J., & Anthenelli, R. M.	1	serotonin transporter (5-HTTLPR) genotype					
50	2012	GABRA2 and KIBRA genotypes predict early relapse to substance use. Bauer, L. O., Covault, J., & Gelernter, J.	3	GABRA2	KIBRA	BDNF			
51	2013	Interactive effects of chronic cigarette smoking and age on hippocampal volumes. Durazzo, T. C., Meyerhoff, D. J., & Nixon, S. J.	2	GABA	glutamate				
52	2013	Examining the association of NRXN3 SNPs with borderline personality disorder phenotypes in heroin dependent cases and socio-economically disadvantaged controls. Panagopoulos, V. N., Trull, T. J., Glowinski, A. L., Lynskey, M. T., Heath, A. C., Agrawal, A., ... & Nelson, E. C.	1	NRXN3 SNPs					
53	2013	NKAIN1–SERINC2 is a functional, replicable and genome-wide significant risk gene region specific for alcohol	3	SERINC2	KIAA0040	IPO11			

		dependence in subjects of European descent. Zuo, L., Wang, K., Zhang, X. Y., Krystal, J. H., Li, C. S. R., Zhang, F., ... & Luo, X.							
54	2013	Serotonin transporter and receptor genes significantly impact nicotine dependence through genetic interactions in both European American and African American smokers. Yang, Z., Seneviratne, C., Wang, S., Ma, J. Z., Payne, T. J., Wang, J., & Li, M. D.	3	SLC6A4	5-HT(3AB) subunit HTR3A	5-HT(3AB) subunit HTR3B			
55	2013	Abuse liability and reinforcing efficacy of oral tramadol in humans. Babalonis, S., Lofwall, M. R., Nuzzo, P. A., Siegel, A. J., & Walsh, S. L.	1	mu-opioid receptor					
56	2013	Accentuating effects of nicotine on ethanol response in mice with high genetic predisposition to ethanol-induced locomotor stimulation. Gubner, N. R., McKinnon, C. S., Reed, C., & Phillips, T. J.	2	Chrna6	Chrna4				
57	2013	Case–control association analysis of polymorphisms in the delta-opioid receptor, OPRD1, with cocaine and opioid addicted populations. Crist, R. C., Ambrose-Lanci, L. M., Vaswani, M., Clarke, T. K., Zeng, A., Yuan, C., ... & Berrettini, W. H.	2	delta-opioid receptor, OPRD1	rs678849				

58	2014	Genome-wide survival analysis of age at onset of alcohol dependence in extended high-risk COGA families. Kapoor, M., Wang, J. C., Wetherill, L., Le, N., Bertelsen, S., Hinrichs, A. L., ... & Goate, A.	3	rs2168784 on chromosome 3	ARL15 gene	UTP20 gene			
59	2014	History of cigarette smoking in cognitively-normal elders is associated with elevated cerebrospinal fluid biomarkers of oxidative stress. Durazzo, T. C., Mattsson, N., Weiner, M. W., Korecka, M., Trojanowski, J. Q., Shaw, L. M., & Alzheimer's Disease Neuroimaging Initiative	1	APOE4					
60	2014	Ethnic and genetic factors in methadone pharmacokinetics: A population pharmacokinetic study. Bart, G., Lenz, S., Straka, R. J., & Brundage, R. C.	1	rs2032582 and rs3745274 variants of CYP2B6					
61	2014	DSM-5 cannabis use disorder: A phenotypic and genomic perspective. Agrawal, A., Lynskey, M. T., Bucholz, K. K., Kapoor, M., Almasy, L., Dick, D. M., ... & Bierut, L. J.	3	C17orf58	BPTF	PPM1D			
62	2014	Nicotine dependence as a moderator of genetic influences on smoking cessation treatment outcome. Leventhal, A. M., Lee, W., Bergen, A. W., Swan, G. E.,	1	DBH SNPs					

		Tyndale, R. F., Lerman, C., & Conti, D. V.							
63	2014	Monoamine polygenic liability in health and cocaine dependence: Imaging genetics study of aversive processing and associations with depression symptomatology. Moeller, S. J., Parvaz, M. A., Shumay, E., Wu, S., Beebe-Wang, N., Konova, A. B., ... & Goldstein, R. Z.	2	5-HTTLPR (SLC6A4 promoter)	MAOA				
64	2014	Randomized clinical trial of disulfiram for cocaine dependence or abuse during buprenorphine treatment. Schottenfeld, R. S., Chawarski, M. C., Cubells, J. F., George, T. P., Lappalainen, J., & Kosten, T. R.	1	SNP inhibiting dopamine β-hydroxylase (DβH).					
65	2014	Who benefits from additional drug counseling among prescription opioid-dependent patients receiving buprenorphine–naloxone and standard medical management? Weiss, R. D., Griffin, M. L., Potter, J. S., Dodd, D. R., Dreifuss, J. A., Connery, H. S., & Carroll, K. M.	1	mu-opioid receptor (OPRM1)					
66	2014	DRD4 and susceptibility to peer influence on alcohol use from adolescence to adulthood. Mrug, S., & Windle, M.	1	DRD4					
67	2014	The effects of chronic alcohol self-administration on serotonin-1A receptor binding in nonhuman primates.	1	serotonin-1A receptor					

		Hillmer, A. T., Wooten, D. W., Tudorascu, D. L., Barnhart, T. E., Ahlers, E. O., Resch, L. M., ... & Christian, B. T.							
68	2014	The impact of lifetime drug use on hepatitis C treatment outcomes in insured members of an integrated health care plan. Russell, M., Pauly, M. P., Moore, C. D., Chia, C., Dorrell, J. M., Cunanan, R. J., & Witt, G.	1	HCV					
69	2014	Subjective response to alcohol and associated craving in heavy drinkers vs. alcohol dependents: An examination of Koob's allostatic model in humans. Bujarski, S., & Ray, L. A.	1	OPRMI Asp40					
70	2014	Interplay of genetic risk (CHRNA5) and environmental risk (partner smoking) on cigarette smoking reduction. Chen, L. S., Baker, T. B., Piper, M. E., Smith, S. S., Gu, C., Grucza, R. A., ... & Bierut, L. J.	1	CHRNA5					
71	2015	Hepatitis C virus infection and pain sensitivity in patients on methadone or buprenorphine maintenance therapy for opioid use disorders. Tsui, J. I., Lira, M. C., Cheng, D. M., Winter, M. R., Alford, D. P., Liebschutz, J. M., ... & Samet, J. H.	1	HCV					
72	2015	Buspirone treatment of cannabis dependence: A randomized, placebo-controlled trial. McRae-Clark, A. L., Baker, N. L., Gray, K. M., Killeen, T. K.,	1	5-HT1A receptor genotype					

		Wagner, A. M., Brady, K. T., ... & Norton, J.							
73	2015	Crystal methamphetamine use and HIV medical outcomes among HIV-infected men who have sex with men accessing support services in New York. Feldman, M. B., Thomas, J. A., Alexy, E. R., & Irvine, M. K.	1	CD4 cell count					
74	2015	Using behavioral economics to predict opioid use during prescription opioid dependence treatment. Worley, M. J., Shoptaw, S. J., Bickel, W. K., & Ling, W.	1	DRD2/ANKK1 Taq IA					
75	2015	Variations in opioid receptor genes in neonatal abstinence syndrome. Wachman, E. M., Hayes, M. J., Sherva, R., Brown, M. S., Davis, J. M., Farrer, L. A., & Nielsen, D. A.	2	PNOC rs732636	OPRK1 rs702764	OPRM1	COMT	OPRD1	
76	2016	Involvement of delta opioid receptors in alcohol withdrawal-induced mechanical allodynia in male C57BL/6 mice. Alongkronrusmee, D., Chiang, T., & van Rijn, R. M.	1	delta opioid receptors					
77	2016	Differences in IV alcohol-induced dopamine release in the ventral striatum of social drinkers and nontreatment-seeking alcoholics. Yoder, K. K., Albrecht, D. S., Dzemidzic, M., Normandin, M. D., Federici, L. M., Graves, T., ... & Kareken, D. A.	1	OPRM1 A118G					

78	2016	Polygenic risk scores for cigarettes smoked per day do not generalize to a Native American population. Otto, J. M., Gizer, I. R., Bizon, C., Wilhelmsen, K. C., & Ehlers, C. L.	3	nAChR genes	CYP2A6 and CYP2B6	CHRNB3 and CHRNA6			
79	2016	The effects of alcohol on spontaneous clearance of acute hepatitis C virus infection in females versus males. Tsui, J. I., Mirzazadeh, A., Hahn, J. A., Maher, L., Bruneau, J., Grebely, J., ... & Page, K.	2	HCV	IFNL4				
80	2016	A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence. Carroll, K. M., Nich, C., Petry, N. M., Eagan, D. A., Shi, J. M., & Ball, S. A.	1	rs1611115					
81	2016	Alcohol use and hepatitis C virus treatment outcomes among patients receiving direct antiviral agents. Tsui, J. I., Williams, E. C., Green, P. K., Berry, K., Su, F., & Ioannou, G. N.	1	HCV					
82	2017	Phenotypic and familial associations between childhood maltreatment and cannabis initiation and problems in young adult European-American and African-American women. Grant, J. D., Agrawal, A., Werner, K. B., McCutcheon, V.	1	CHRNA2					

		V., Nelson, E. C., Madden, P. A., ... & Sartor, C. E.							
83	2017	Environmental risks outweigh dopaminergic genetic risks for alcohol use and abuse from adolescence through early adulthood. Coley, R. L., Sims, J., & Carrano, J.	1	Taq1 A1 allele of the dopamine D2 receptor gene					
84	2017	Structural deficits in salience network regions are associated with increased impulsivity and compulsivity in alcohol dependence. Grodin, E. N., Cortes, C. R., Spagnolo, P. A., & Momenan, R.	1	(not a gene) VENs neurons					
85	2018	Cost-effectiveness of hepatitis C screening and treatment linkage intervention in US methadone maintenance treatment programs. Schackman, B. R., Gutkind, S., Morgan, J. R., Leff, J. A., Behrends, C. N., Delucchi, K. L., ... & Linas, B. P.	1	HCV					
86	2018	Is the Fagerström test for nicotine dependence invariant across secular trends in smoking? A question for cross-birth cohort analysis of nicotine dependence. Glasheen, C., Johnson, E. O., Saccone, N. L., Lutz, S. M., Baker, T. B., McNeil, D. W., ... & Hancock, D. B.	1	nicotinic acetylcholine receptor gene [CHRNA5] variant rs16969968					
87	2018	The interplay between externalizing disorders polygenic risk scores and	~	genome-wide					

		contextual factors on the development of marijuana use disorders. Rabinowitz, J. A., Musci, R. J., Milam, A. J., Benke, K., Uhl, G. R., Sisto, D. Y., ... & Maher, B. S.		associatio n studies					
88	2018	Nicotine metabolite ratio predicts smoking topography: The Pennsylvania T Adult Smoking Study. Chen, A., Krebs, N. M., Zhu, J., & Muscat, J. E.	1	CYP2A6					
89	2018	'Hep C's like the common cold'_ understanding barriers along the HCV care continuum among young people who inject drugs. Skeer, M. R., Ladin, K., Wilkins, L. E., Landy, D. M., & Stopka, T. J.	1	HCV					
90	2018	Dating violence victimization and substance use: The role of a serotonin transporter gene polymorphism (5 HTTLPR). Yohros, A., Ford, J., & Hinojosa, M. S.	1	5 HTTLPR					
91	2019	Neuroimaging findings from an experimental pharmacology trial of naltrexone in heavy drinkers of East Asian descent. Lim, A. C., Ghahremani, D. G., Grodin, E. N., Green, R., Bujarski, S., Hartwell, E. E., ... & Ray, L. A.	1	OPRM1					
92	2019	Age of initiation and transition times to tobacco dependence: Early onset T and rapid escalated	1	mu opioid receptor genes					

		use increase risk for dependence severity. Huggett, S. B., Keyes, M., Iacono, W. G., McGue, M., Corley, R. P., Hewitt, J. K., & Stallings, M. C.							
93	2019	Relationship between skin melanin index and nicotine pharmacokinetics in African American smokers. Liakoni, E., Helen, G. S., Dempsey, D. A., Jacob III, P., Tyndale, R. F., & Benowitz, N. L.	1	CYP2A6					
94	2019	The etiology of DSM-5 alcohol use disorder: Evidence of shared and non-shared additive genetic effects. Palmer, R. H., Brick, L. A., Chou, Y. L., Agrawal, A., McGeary, J. E., Heath, A. C., ... & Knopik, V. S.	3	h2SNP	rGSNP	ADH1B			
95	2019	Associations between drug use patterns and viral load suppression among T HIV-positive individuals who use support services in New York City. Feldman, M. B., Kepler, K. L., Irvine, M. K., & Thomas, J. A.	1	CD4 cell count					
96	2020	Genome-wide association analysis of opioid use disorder: A novel approach using clinical data. Song, W., Kossowsky, J., Torous, J., Chen, C. Y., Huang, H., Mukamal, K. J., ... & Wright, A.	6	KCNC1	KCNG2	CNIH3	OPRM1	RGMA	SLC30A9

97	2020	Independent association of tobacco use with opioid use disorder in patients of European ancestry with chronic non-cancer pain. Cheatle, M. D., Falcone, M., Dhingra, L., & Lerman, C.	1	OPRM1					
98	2020	Stability in effects of different smoking-related polygenic risk scores over T age and smoking phenotypes. Deutsch, A. R., & Selya, A. S.	3	CHRNA5	CYP2A6	DRD2/ANKK1			
99	2020	A prospective study of the association between rate of nicotine metabolism and alcohol use in tobacco users in the United States. Roberts, W., Marotta, P. L., Verplaetse, T. L., Peltier, M. R., Burke, C., Ramchandani, V. A., & McKee, S. A.	1	CYP2A6					
100	2021	Perceived social support in patients with chronic pain with and without opioid use disorder and role of medication for opioid use disorder. Benville, J. R., Compton, P., Giordano, N. A., & Cheatle, M. D.	1	delta opioid receptors					
101	2021	Effect of HIV, antiretrovirals, and genetics on methadone pharmacokinetics: Results from the methadone antiretroviral pharmacokinetics study. Bart, G., Yen, H., Hodges, J. S., & Brundage, R. C.	3	CYP2B6	ABCB1	NR1I3			
102	2021	Ancestry may confound genetic machine learning: Candidate-	1	OPRM1					

		gene prediction of opioid use disorder as an example. Hatoum, A. S., Wendt, F. R., Galimberti, M., Polimanti, R., Neale, B., Kranzler, H. R., ... & Agrawal, A.							
103	2021	Cannabis use in college: Genetic predispositions, peers, and activity participation. Thomas, N. S., Salvatore, J. E., Gillespie, N. A., Aliev, F., Ksinan, A. J., Dick, D. M., & Spit for Science Working Group.	1	CADM2					
104	2021	Hnrnph1 is a novel regulator of alcohol reward. Fultz, E. K., Coelho, M. A., Lieberman, D., Jimenez-Chavez, C. L., Bryant, C. D., & Szumlinski, K. K.	1	Hnrnph1					
105	2021	Nicotine metabolite ratio: Comparison of the three urinary versions to the plasma version and nicotine clearance in three clinical studies. Giratallah, H. K., Chenoweth, M. J., Addo, N., Ahluwalia, J. S., Cox, L. S., Lerman, C., ... & Tyndale, R. F.	3	CYP2A6	UGT2B10	UGT2B17			
106	2021	Racial disparities in intensity of smoke exposure and nicotine intake among low-dependence smokers. Ho, J. T., Tyndale, R. F., Baker, T. B., Amos, C. I., Chiu, A., Smock, N., ... & Chen, L. S.	1	UGT2B10					
107	2021	A randomized, double-blind, placebo-controlled trial of ondansetron for the treatment of	2	HTR3A	HTR3B				

		cocaine use disorder with post hoc pharmacogenetic analysis Blevins, D., Seneviratne, C., Wang, X. Q., Johnson, B. A., & Ait-Daoud, N..							
108	2021	Age and gender-specific hepatitis C continuum of care and predictors of direct acting antiviral treatment among persons who inject drugs in Seattle, Washington. orcorran, M. A., Tsui, J. I., Scott, J. D., Dombrowski, J. C., & Glick, S. N.	1	HCV					
109	2021	Analysis of genetic and clinical factors associated with buprenorphine response. Crist, R. C., Vickers-Smith, R., Kember, R. L., Rentsch, C. T., Xu, H., Edelman, E. J., ... & Kranzler, H. R.	6	SLC25A37	NNT/FGF10	FAM20C	CRISPLD2	LINC01947	ADAMTSL2
110	2022	Effects of genetic risk for alcohol dependence and onset of regular drinking on the progression to alcohol dependence: A polygenic risk score approach. Yeung, E. W., Spychala, K. M., Miller, A. P., Otto, J. M., Deak, J. D., Kim, H., ... & Gizer, I. R.	~	genome-wide association studies					
111	2022	Relationship between depressive symptoms and adherence to direct-acting antivirals: Implications for Hepatitis C treatment among people who inject drugs on medications for opioid use disorder.	1	HCV					

		Pericot-Valverde, I., Heo, M., Niu, J., Rennert, L., Norton, B. L., Akiyama, M. J., ... & Litwin, A. H.							
112	2022	Alcohol consumption upon direct-acting antiviral therapy for hepatitis C among persons with human immunodeficiency virus in the United States. Chen, P. H., Yenokyan, K., Fojo, A. T., Hutton, H. E., Lesko, C. R., McCaul, M. E., ... & Chander, G.	1	HCV					
113	2022	Alcohol use and alcohol use disorder differ in their genetic relationships with PTSD: A genomic structural equation modeling approach. Bountress, K. E., Brick, L. A., Sheerin, C., Grotzinger, A., Bustamante, D., Hawn, S. E., ... & Psychiatric Genomics Consortium Posttraumatic Stress Disorder Working Group.	1	SNPs					
114	2022	Associations between cognition and polygenic liability to substance involvement in middle childhood: Results from the ABCD study. Paul, S. E., Hatoum, A. S., Barch, D. M., Thompson, W. K., Agrawal, A., Bogdan, R., & Johnson, E. C.	~	genome-wide association study					
115	2023	Genetic predisposition to major depressive disorder differentially impacts alcohol consumption and high-risk drinking situations	~	genome-wide association studies					

		in men and women with alcohol use disorder. Kapoor, M., Wang, J. C., Wetherill, L., Le, N., Bertelsen, S., Hinrichs, A. L., ... & Goate, A.							
116	2023	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. Wang, F. L., Hicks, B. M., Zhou, H., Kranzler, H. R., Gelernter, J., & Zucker, R. A.	~	genome-wide association studies					
117	2023	The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5): Reliability of substance use and psychiatric disorder modules in a general population sample. Grant, B. F., Goldstein, R. B., Smith, S. M., Jung, J., Zhang, H., Chou, S. P., ... & Hasin, D. S.	1	ADH1B					
118	2023	Associations of polygenic risk scores for smoking heaviness and lifetime cannabis use with tobacco and cannabis co-use trajectories among cannabis use with tobacco and cannabis co-use trajectories among. Rabinowitz, J. A., Reboussin, B. A., Sosnowski, D. W., Sally, I., Kuo, C., Strickland, J. C., ... & Uhl, G.	~	genome-wide association study					

119	2023	BDNF rs6265 Met carriers with alcohol use disorder show greater age-related decline of N-acetylaspartate in left dorsolateral prefrontal cortex. Durazzo, T. C., McNerney, M. W., Hansen, A. M., Gu, M., Sacchet, M. D., & Padula, C. B.	1	BDNF rs6265 Met					
120	2023	The relationship between alcohol- and sleep-related traits: Results from polygenic risk score and Mendelian randomization analyses. Chakravorty, S., Kember, R. L., Mazzotti, D. R., Dashti, H. S., Toikumo, S., Gehrman, P. R., & Kranzler, H. R.	~	genome-wide association studies					

Appendix B: Behavioral and Health Outcomes

ID	# of Behavioral Outcomes	Behavioral Outcome_1	Behavioral Outcome_2	Behavioral Outcome_3	Health Outcome? (Y/N)	Health Outcome(s)
1	1	cannabis dependence			No	N/A
2	1	methadone			Yes	hepatitis C infection
3	1	heroin use			Yes	chronic pain
4	1	substance dependence vulnerability			No	N/A
5	2	intranasal consumption of cocaine	methadone (opioid treatment)		Yes	cirrhosis, liver disease
6	1	general substance abuse			Yes	hepatitis C infection
7	1	alcohol use			Yes	chronic stress
8	1	substance use			Yes	personality disorder
9	1	cocaine dependency			Yes	paranoia
10	1	substance abuse			Yes	antisocial personality disorder
11	1	cannabis withdrawal			Yes	anxiety; aggression; irritability; depression
12	1	general substance abuse			No	ADHD, panic disorder, major depressive disorder, bipolar disorder
13	1	alcohol use disorder			Yes	conduct disorder
14	2	alcohol dependence	nicotine dependence		Yes	major depressive disorder; panic attack, and generalized anxiety disorder
15	1	alcohol use			Yes	severe conduct disorder
16	1	cannabis dependence			No	N/A
17	2	illicit drug dependence	alcohol dependence		Yes	conduct disorder
18	1	drug resistance			Yes	HIV
19	1	heroin dependence			No	N/A
20	1	general substance abuse			Yes	ADHD
21	1	nicotine smoking cessation			No	N/A

22	1	heroin injection			Yes	HIV/AIDS diagnosis
23	1	nicotine dependence phenotypes			No	N/A
24	1	substance use disorder			Yes	conduct disorder
25	3	cannabis dependence	alcohol dependence	illicit drug use	No	N/A
26	1	morphine withdrawal			No	N/A
27	1	general substance abuse			No	N/A
28	1	morphine use			Yes	locomotor activity
29	1	methadone			Yes	hepatitis C infection
30	1	alcohol craving			No	N/A
31	1	cannabis dependence			No	N/A
32	1	smoking/ tobacco dependence			No	N/A
33	1	alcoholism			Yes	N/A
34	1	marijuana dependence			Yes	antisocial personality disorder; conduct disorder
35	1	methamphetamine dependence			Yes	ADHD and depression
36	1	oxycodone use			No	N/A
37	1	alcohol abuse			Yes	liver disease;
38	1	alcohol use disorder			Yes	antisocial personality disorder, conduct disorder
39	1	alcohol dependence			No	depression; anxiety disorder
40	1	alcohol dependence			Yes	anxiety disorder, PTSD, eating disorders
41	2	tobacco dependence	alcohol use disorder		Yes	HIV sexual risk; conduct disorder
42	1	injection drug use			Yes	cirrhosis, end-stage liver disease and liver cancer cases
43	3	alcohol abuse	general substance abuse	regular tobacco use	Yes	impulsivity
44	1	nicotine dependence			Yes	major depressive disorder, posttraumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), conduct disorder, and antisocial personality disorder (ASPD)

45	1	nicotine dependence			Yes	cancer (lung cancer deaths); comorbidities = major depression, anxiety, ADHD, PTSD, schizophrenia
46	1	nicotine dependence			Yes	tobacco-related deaths
47	2	toluene abuse	alcohol abuse		Yes	locomotor impairment
48	2	development of cannabis use disorder			Yes	deviance/ problem behavior syndrome; depression; social anxiety disorder
49	2	risk for cigarette smoking/nicotine dependence	alcohol dependence		Yes	childhood adversity/ maltreatment
50	1	substance use relapse			No	N/A
51	1	chronic cigarette smoking			Yes	memory impairment
52	1	heroin dependency			Yes	borderline personality disorder
53	1	alcohol dependence			No	N/A
54	1	nicotine dependence			Yes	psychiatric disorders
55	2	opioid abuse	tramadol use (to mimic opioid abuse)		No	N/A
56	2	nicotine consumption	alcoholism		No	N/A
57	2	cocaine abuse	nicotine dependence		No	N/A
58	1	alcohol dependence			No	N/A
59	1	cigarette smoking			No	N/A
60	1	methadone			No	N/A
61	1	cannabis use disorder			No	N/A
62	1	nicotine dependence			No	N/A
63	1	cocaine dependence			Yes	major depressive disorder
64	1	cocaine dependence			No	N/A
65		opioid dependence			Yes	chronic pain
66	1	alcohol use			No	N/A
67	1	chronic alcohol self-administration			No	N/A
68	1	general substance abuse			Yes	hepatitis C infection
69	1	alcohol dependency	heavy drinking		No	N/A

70	1	cigarette smoking reduction			No	N/A
71	1	opioid use disorders			Yes	hepatitis C infection; chronic pain
72	1	cannabis dependence			Yes	anxiety disorders
73	1	crystal methamphetamine use			Yes	HIV
74	1	opioid dependence			Yes	chronic pain
75	1	opioid abuse/exposure			Yes	neonatal abstinence syndrome
76	1	alcohol withdrawal			Yes	allodynia
77	1	social alcohol consumption			No	N/A
78	1	cigarette smoking			No	N/A
79	1	alcohol use			Yes	hepatitis C infection, HIV
80	2	cocaine dependence	disulfiram use		Yes	cognitive dysfunction
81	1	alcoholism			Yes	liver cancer, cirrhosis, hepatitis C viral infection
82	1	cannabis initiation			No	N/A
83	1	alcohol abuse			Yes	chronic stress
84	1	alcohol dependence			Yes	increased impulsivity and compulsivity
85	1	methadone			Yes	hepatitis C infection
86	1	nicotine dependence			No	N/A
87	1	marijuana use disorders			Yes	conduct disorder; ADHD
88		nicotine dependence			No	N/A
89	1	Abuse of injected drugs			Yes	hepatitis-C viral infection
90	2	alcohol use	marijuana use		No	N/A
91	1	alcohol consumption			No	N/A
92	1	tobacco dependence			No	N/A
93	1	nicotine use			No	N/A
94	1	alcohol use disorder			No	N/A
95	1	general substance abuse			Yes	HIV
96	1	opioid use disorder			No	N/A
97	1	opioid use disorders			Yes	chronic pain; anxiety

98	1	smoking phenotypes			No	N/A
99	2	alcohol use	tobacco use		Yes	physical withdrawal, social problems, issues with school/at work
100	1	opioid use disorder			Yes	chronic pain
101	1	opioid use disorder			Yes	HIV infection
102	1	opioid use disorder			No	N/A
103	1	cannabis use			Yes	academic function and cognition
104	1	alcohol reward response			Yes	dysphoria
105	1	nicotine use			No	N/A
106	1	nicotine intake			No	N/A
107	1	cocaine use disorder (CUD)			No	N/A
108	1	drug injection (heroin, methamphetamine)			Yes	HIV
109	2	opioid use disorder	buprenorphine treatment exposure		Yes	major depressive disorder
110	1	alcohol dependence			No	N/A
111	1	opioid use disorder			Yes	hepatitis C infection; major depressive disorder
112	1	alcohol consumption			Yes	HIV
113	1	alcohol use disorder	alcohol consumption		Yes	PTSD
114	1	alcohol abuse			Yes	N/A
115	1	alcohol use disorder			Yes	major depressive disorder
116	1	alcohol use disorder			Yes	childhood maltreatment
117	1	alcohol use disorder			Yes	mood; anxiety; PTSD
118	2	chronic tobacco use	cannabis use		No	N/A
119	1	alcohol use disorder			No	N/A
120	1	alcohol use disorder			Yes	insomnia

Appendix C: Study Limitations and Sample Demographics

ID	Sample Age	Sample Size	Study Limitations? (Y/N)	Limitation_1	Limitation_2	Limitation_3	Limitation_4
1	mean age = 18.2	n = 3481	Yes	study's estimates are based upon retrospective recall of the age of onset of individual clinical features, and are subject to errors of recall and accuracy in reporting	lack of generalizability: replications in other samples are needed to clarify whether similar results will be seen elsewhere		
2	32-66 years (average 50)	50	Yes	the study's lack of a comparison group and its small sample size limit firm statistical comparisons, and larger-scale study is warranted			
3	N/A	N/A	Yes	heroin and morphine have different time courses, and the potential contribution of pharmacokinetic factors to measures of in vivo apparent efficacy have not been examined	calculations of in vivo apparent efficacy were based on agonist dose-effect curves determined after treatment with only one dose of the irreversible antagonist	solubility of morphine precluded assessment of higher morphine doses that might have produced greater effects	
4	adolescent (13-19), (12-25)	500 (250 sibling pairs); community-based	Yes	power to detect QTL in low effect sizes is limited	not all subjects have experience with substance abuse or polysubstance abuse.	sample for study is selected for problem substance abuse and conduct disorder - unable to generalize to broader populations.	approach used is more specific to identifying the QTL underlying general risk factors that can be shared among multiple risk factors as opposed to the

		samples: 3676					QTL that influence responses or susceptibility to certain drugs.
5	adults	256 treatment units (avg. 163 patients, SD =167)	Yes	Although respondents were asked to complete worksheets eliciting information about HCV antibody testing, some did not do so	data reflects the provision of HCV related services by drug treatment units as reported by an administration or medical staff member, not by interviewing patients	Possibility that non-participating units differ drastically from those interviewed	
6	average age = 48 years	500	Yes	results were from a single testing session	screening program is referral-based rather than population based, potentially skewing the testing results toward patients with a higher medical acuity and altering the demographics	patients may be older than and differ ethnically from other substance using populations with HCV and may have had lengthier viral exposure	
7	adolescents, mean age at beginning of study = 16.14/ mean age at end of study = 22.45	n = 12,136	Yes	the model-fitting results provide broad estimates of the relative influence of genetic and environmental factors as indicated by the confidence intervals around the point estimates	due to the small effect size of single genetic polymorphisms, it is likely that this study has inadequate statistical power to reject the null hypothesis of no association		
8	adolescent (mean age = 16.2 years)	48	Yes	this is a preliminary study	data used only came from Caucasian and Hispanic boys	small sample size	

9	adults, mean age = 38.5 years	n = 273	Yes	the heritability of CIP is likely to be less than the heritability of alcohol dependence, or less than 0.50	ample was not an epidemiologic one, and thus, sampling biases certainly have the potential to influence our findings	study is limited by the largely retrospective nature of our structured assessment instrument and our inability to infer causal associations between traits/variables of interest	limitations of sample size and study design
10	adult adoptees	n =247	Yes	sample was 94.1% Caucasian	substantial refusal rate for genetic data collection	lack of ability to stratify or control in detail for possible confounding by ethnic subgroups	lack of statistical power for resolving additive versus dominant allele associations or a distinction between depression risk specific to alcoholism instead of other associated conditions.
11	adults, mean = 32.5 years	n = 8	Yes	small sample size of mostly males	possible that participants used small amounts of cannabis during the abstinence conditions that went undetected	it is unknown how these findings generalize to treatment seekers	
12	mean age = 42.3 years	n = 1879	Yes	probands were clinically referred, so results may not generalize to population samples	secondary analysis of several data sets, each of which had been collected to test other primary hypotheses		
13	ages 13–19	n = 239	Yes	patients with AUD and controls were adolescents	most analyses were completed with alcohol use disorders and not with alcohol dependence alone		

14	12 to 26 years (mean 20.1 ± 4.0 years)	732 twin pairs	Yes	inability to fully determine the direction of the causal relationship between comorbid AD and ND as well as between these dependencies and child psychopathology	did not explore the interaction of child psychopathology, age, and gender on risk for AD	findings indicate that both genetic and environmental influences contribute to risk for AD and ND	
15	13–19-year-old (adolescents)	418 (239 with substance abuse problems)	Yes	Patients were adolescents, and research shows that the peak onset of alcohol dependence is now 18 years of age	Most analyses were completed with alcohol use disorders and not with alcohol dependence alone	Lacked power to detect a more modest association between the A1 allele and alcohol use disorders	
16	adolescent (13-19), (12-25)	648 (324 sibling pairs)	Yes	ability to detect small effect sizes commonly found in psychiatric disorders is limited in linkage analysis			
17	age 24-37	9577	Yes	sample of adult Caucasians and findings may not generalize to other ethnic groups	study included nicotine and cannabis experimenters instead of restricting the analyses to those with more substantial exposure		
18	N/A	N/A	Yes	limited to only HIV dynamic models			
19	adults, (PND56-70)	N/A	Yes	alcohol reward phenotype of Hnrnph1 mutants is unrelated to changes in sensitivity to any of alcohol's effects on motor behavior or alcohol metabolism	lack of genotypic differences in alcohol-induced locomotion may reflect procedural differences related to the duration of locomotor testing		

20	mean age = 14.0 year	n = 2,743	Yes	probands were clinically referred, therefore results may not generalize to population samples	this is a secondary analysis of several data sets, each of which had been collected to test other primary hypotheses		
21	mean age = 46.7 years	n = 393	Yes	prospect of potentially tailoring NRT based on serotonergic genotypes appears unlikely to materialize	possibility that serotonergic pharmacotherapies such as SSRIs or buspirone, which have not demonstrated efficacy for smoking cessation may be efficacious for subgroups defined by genetic variants in the 5-HT pathway		
22	mean age = 33.3 years	n = 2252	Yes	routine efforts to improve TEDS may account for some historical variation in the data.	the extent to which TEDS covers admissions data is affected by differences in State systems of licensure, certification, accreditation, and disbursement of public funds and the data set may underrepresent persons receiving treatment in private programs		
23	adults, mean age = 41.9 years	n = 1,289	Yes	no built-in replication sample	sample was ascertained on the	variance components linkage analyses	

					basis of alcohol dependence	required assumptions of trait normality	
24	adolescence	(462 - controls = 231, cases = 231)	Yes	lack of power to cleanly identify any SNPs with genome-wide significance			
25	range 17-91 years (mean age= 40.6)	1214 Caucasians, 150 African Americans for linkage analysis	Yes	significant overlap between the high-risk families that contributed to the linkage signal for alcohol dependence and the families for illicit drug dependence criteria	Overlap of linkage findings is likely due to the high comorbidity in the sample	Community-based sample was ascertained from various sources	Relatively small proportion of African American families which did not allow for sufficient power to conduct linage analyses independently in these samples.
26	N/A	N/A	No				
27	mean age = 14.52	n = 1,377	Yes	the cross-sectional nature of this sample makes it difficult to evaluate the possible causal relationship between PPD and DV	only considered the role of PPD as a moderator and DV as the phenotypic outcome	use of substance dependence without consideration of substance use	
28	N/A	N/A	No				
29	mean age = 43 years	n = 100	Yes	relatively small sample size of 100 participants; recruitment fact that recruitment took place at only one large Central New York MMT clinic; may limit our ability to generalize the findings to patients in other regions	inclusion of only those patients with some form of Medicaid or other insurance coverage for HCV treatment		
30	older adults, mean age = 61.6 years	n = 95	Yes	limited in scope to individuals 50 years of age and older	subjects taking an antidepressant were allowed in the study, but there was no		

					association with being on an antidepressant and class assignment nor was the class assignment associated with staying on an antidepressant		
31	young adults (184-18.8 mean age)	332 (75% Caucasian, 15% Hispanic, and 10% Other/Biracial ethnicity); 64% male	Yes	numerous factors that can influence association study results, including sampling, linkage disequilibrium patterns, and effect size	significant portion of the sample is comprised of youth with polysubstance dependence and conduct problems	sample is not representative of the general population	
32	young adult	N = 169	Yes	most findings are from post-hoc analysis of a small sample			
33	18-26, mean = 21.91	n = 15,197	Yes	the genetic polymorphism data were collected from only a subsample of respondents in the Add Health study	the analyses did not examine potential interactive effects between polymorphisms	the alcoholic father measure was not based on a clinical diagnosis of alcohol abuse or dependence	the current study cannot address the molecular mechanisms that underlie the relationship between DAT1 and serious alcohol problems.
34	mean age = 28.0	n = 626	Yes	the findings may not generalize to other Native Americans or represent all Indians within this population	only retrospective and cross-sectional data on MJ, ALC and other drug use disorders were assessed		
35	mean age 39.1	n = 71	Yes	powered to detect at least a moderate effect for modafinil (d = 0.50) in the overall sample assuming that a medication lacking at			

				least a moderate sized effect in the overall sample would lack clinical significance			
36	adults (mean age = 28)	9 (5 men, 4 women; 5 White, 1 Black, 1 Hispanic, 1 Asian, 1 Indian)	Yes	data must be viewed with caution, however, because of the small sample sizes in each group			
37			Yes	underlying mechanisms responsible for the alcohol effect on HCV replication are still not determined			
38	13-18 years old	n=1582 (Patient siblings (n = 245), parents of patients (n = 355), adolescent controls (n = 185), siblings of controls (n = 163) and parents of controls (n = 263)	Yes	Only tested a single SNP in the GABRA2 gene	Family-based analyses had only 66% power		
39	adults, mean age = 49.9	n = 1,647	Yes	the present study was designed to detect loci with moderate effects	likely that additional genetic loci that exhibited only a small effect on alcohol dependence		

					in the UCSF sample were missed		
40	adults, mean age = 46.98	n = 131	Yes	recruited from urban clinics, inability to make generalizations	study relied upon retrospective assessment of abuse status, alcohol behaviors, and psychiatric problems		
41	adults (age 24)	n = 808	Yes	measures of adolescent family environment were averaged across late childhood and adolescence	relied on self-reports of substance use disorders, crime, and HIV sexual risk behavior that may be susceptible to social desirability bias	SUD assessed with a widely-used, standardized questionnaire	
42	adults (18-35 years of age)	cross-sectional analysis = 113; longitudinal analysis = 72	Yes	temporal relationship between risk behaviors and HCV chronicity cannot be firmly established for the cross-sectional analysis	socially desirable responding regarding injection behaviors is probable	misclassification of chronic infection is possible (though not likely, given the stringent criteria used for classification including the requirement of detectable viral load for at least two study visits)	
43	Age ranged from 18 to 67 (Mean = 22.49, SD = 6.12; 81.6% were age 24 or younger	n = 439	Yes	more detailed examination of phenotypes of addiction and genetic variation across NRXN3	p-values were not corrected; sample sizes were relatively small	definitions for substance use problems/alcohol abuse were subjective: not a diagnosis. moreso a criteria or metric of problematic substance use	
44	ages 25–44	2032 subjects of	Yes	NIH grants P01 CA089392; KL2RR023249 and	NIDA grants R01DA026911 and K08DA030398		

		European descent		K08DA030398 by NIH/NCRR			
45	adults	792 from COGA, 1667 Caucasian individuals from FSCD and COGEND sample	Yes	no SNP reached the genome-wide significance level	only had two samples for the meta-analysis		
46	adults	24 (14 A allele/10 G/G allele)	Yes	relatively small sample size	limited to women (does this genotype occur in men)	3 non-Caucasian smokers	womens hormonal status not taken into consideration
47	N/A	N/A	Yes	one possibility is that loss of function of unc-79 is causing a non-specific effect that alters responses to all of these CNS depressant drugs	some specificity must exist because unc-79 mutations do not alter sensitivity to the volatile anesthetic isoflurane under the same conditions where changes in halothane sensitivity are observed		
48	adolescence (10-12 with study ending at age 22)	baseline = 500 boys; follow-up = 254	Yes	sample confined to boys (girls demonstrate greater willingness for cooperative behavior and are more socially responsive than boys are)	confined to evaluating the role of transmissible SUD risk in socialization	model tested was confined to affiliation with deviant peers as a mediator of transmissible risk during childhood and a predictor of cannabis use disorder	outcome variable in this study was circumscribed to cannabis disorder
49	adults (mean age of 45.6)	256; men (n=149), women (n=107);	Yes	Aim of post hoc analysis did not align with the primary aim of the original investigations from	data were not collected on other childhood factors that are associated with increased risk	sample size was relatively small for the analysis of genetic influences	

		Caucasian (n=205)		which the participants were drawn	of both ACEs and cigarette smoking		
50	adults, 20–56 yrs	n=146; 49% female	Yes	small sample size	focus on patients who had psychosocial issues so significant as to bring them to live in a dormitory-like substance abuse treatment facility		
51	adults, mean age = 45	n = 82	Yes	automated hippocampal subfield segmentation was based on a probabilistic atlas derived from sub-millimeter, ultra-high-resolution MRI at 3 T	small sample size	Results may have also been influenced by factors not assessed in this study, such as subclinical biomedical conditions	
52	cases (avg 36.4 years); controls (avg 34.6 years)	1439 cases; 507 controls	Yes	investigation was not designed to comprehensively examine BPD liability	threshold used for a positive screen is low in comparison to the 5 out of 9 symptoms required by DSM-IV	lack of ability to generalize from study sample of opioid dependent cases and neighborhood controls	
53	Adults, Mean age = 34.6	(1409 European-Americans with alcohol dependence; 1518 European-American controls)	Yes	Not all neuropsychiatric and neurological disorders were exhaustively examined in the present study	causal variant within the NKAIN1-SERINC2 region may not be identical to the risk markers implicated in the study (needs further sequencing)		
54	adults	1366 (402 African American, 671 European-Americans)	Yes	NIDA grant DA012844			

55	healthy adults age 18-50 (prescription opioid abusers who were not physically dependent)	14 (9 met criteria)	Yes	No genotyping conducted. However, it is a strong assumption that tramadol is o-demethylated to M1 through the same pathway as opioids such as oxycodone.			
56	adult (PND 60+)	24 mice	Yes	Data shown in Figure 2 suggests additive locomotor depressant effects, but it was not detected significantly. This could be attributed to a floor effect, with significantly lower activity levels difficult to detect.	Possibility that the tendency for increased sedation during this time period is due to effects of an active metabolite of nicotine such as cotinine		
57	adults (mean ages from 36.1 to 51.0)	EA control individuals (n=656; male=50.8%) and AA control individuals (n=503; male= 38.0%), AA control group 2 (n=875; male= 41 %)	Yes	possibility that associations in the AA population are due to population stratification	additional work using ancestry informative markers is needed to determine whether rs678849 is relevant for different ethnic groups		
58	adults, mean age = 22.5 year	n = 1788	Yes	lack of ability to replicate			
59	mean age = 75.5 years	n = 111	Yes	participants were predominately well-	Detailed smoking information was available for 50% of		

				educated elder Caucasians	the participants with a history of smoking		
60	adults, mean age = 40.2	n = 206	Yes	did not have a large prospectively assessed population that would allow us to detect possible methadone autoinduction	used limited pharmacodynamic data such as ongoing drug use or SCL-90 scores but did not perform pharmacokinetic–pharmacodynamic (pk–pd) studies using opiate related measures		
61	mean age = 38.1	n = 3053	Yes	the present sample was ascertained from three family studies of substance use disorders for the express purpose of identifying genetic variants for alcoholism, nicotine and cocaine dependence and related psychopathology	while we were able to include a measure of cannabis withdrawal in the analysis, the symptoms and diagnostic scheme		
62	adult, mean age = 46.8	n = 793	Yes	analysis limited to those who identify as non-Hispanic/White	significance correction for multiple correlated tests is less conservative than a standard Bonferroni adjustment	lacking a sufficient sample to detect three-way interactions between genes, nicotine dependence, and treatment	
63	adults, mean age = 42.4	n = 119	Yes	sample size was relatively small for a genetics study that partitioned the groups by two genotypes and diagnosis	effects should be replicated with samples that include more women	concern of population stratification	

64	age 18-45, mean age = 31.3	n = 177	Yes	conducted with opioid dependent participants receiving buprenorphine maintenance treatment	stringent eligibility criteria	a great number of potential subjects did not want treatment with disulfiram and did not complete the evaluation for study entry	
65	adults (mean age 32.5 years)	n = 360; (90.6%) white (41.9%) female	Yes	individuals who attended more than 60% of treatment sessions, particularly if they were assigned to SMM + ODC, were a self-selected group	cannot conclude that the association between good counseling attendance among heroin users and successful outcome implies that attending counseling leads to a good outcome		
66	mean ages 17 and 33	n = 340; 59% female; 98% White	Yes	self-reports of friend's alcohol use tend to be confounded by their own levels of alcohol use	small sample size		
67	N/A	14 rhesus monkeys	Yes	potential confound of pre-natal alcohol exposure			
68	adults, (< 50 years (45.1%), ≥ 50 years (54.9%))	259	Yes	ascertainment of drug use poses fewer problems concerning memory than retrospective ascertainment, but this advantage is offset by the problems involved in long-term studies of rare chronic diseases	only studied patients who had already been treated to reduce denial		
69	21-29 years of age	91	Yes	cannot definitively assert that heavy	alcohol dependency group did drink	Moderate does of alcohol and the	

				drinkers did not meet criteria for alcohol dependence as diagnostic interviews were not conducted in the HD sample	significantly more than the HD group	assessment along the ascending limb only	
70	adults	n=1856	Yes	Subjects were only of European descent	smoking reports in the ALSPAC sample were not confirmed by biochemical confirmation	targeted approach by choosing to examine the hypothesized interaction between CHRNA5 and partner smoking in two complementary samples without exploring other possible interactions	
71	adults, median age = 45 years	n = 106	Yes	did not adjust for duration of infection with HCV as most patients were unaware of the timing of exposure/infection since patients are typically asymptomatic with acute infection	control group included individuals who spontaneously cleared their infection (n = 23)		
72	N/A	n = 792	Yes	significant attrition during the course of the twelve-week study	long excretion half-life of cannabis in urine	sample size insufficient to detect clinically significant differences	
73	adults, mean age = 35.2	n = 2896	Yes	inability to generalize; HIV-infected individuals in the analysis included only those who received services funded through a Ryan White Part A federal grant to the New	no causality: data are cross-sectional	individuals had to have at least one viral load or CD4 count reported in the Registry within the 3 months prior to completing a substance use assessment	

				York eligible metropolitan area			
74	adults	353	Yes	secondary analysis of a clinical trial for prescription opioid addiction, in which hypotheses not included in the original protocol were examined	drug-related spending and income variables in this study, including the consideration that key variables were captured with the ASI-Lite	assumption that self-reported drug spending was primarily allocated to prescription opioids, when the observed item refers generally to "drugs" without specifying drug type	
75	full-term newborns and their mothers	86 pairs	Yes	Drug exposures are determined by maternal interviews and urine toxicology results	Results based on a relatively small sample	98% of subjects were White (non-Hispanic)	
76	N/A	N/A	No				
77	mean age = 33.9	n = 45	Yes	relatively small sample size	cannot distinguish between a predisposing difference in VST DA function and long-term effects of chronic drinking, a problem common to all neuroimaging studies of addiction		
78	adults (age 22)	n = 775	Yes	target sample size was small	limited power to detect effects across all p-value thresholds		
79	adults (28.5 years)	411 persons (30.4% were women, 87.2% were white)	Yes	cohorts of those with HCV were combined to provide data	limited number of participants who had data on alcohol use	unable to assess whether there is a specific threshold or dose effect of alcohol on spontaneous clearance	

80	18+ years of age (and meeting DSM-IV criteria)	99	Yes	Majority of participants not completing the full course of treatment	Those who dropped out of treatment yielded complete data from 88% of the sample		
81	adults, mostly older adults	17487	Yes	missing SVR data	relies on AUDIT-C screening data to categorize alcohol use	AUDIT-C scores were not drawn immediately at the time of HCV treatment initiation immediately at the time of HCV treatment initiation, so it may not be an accurate reflection of the levels while drinking	sample is largely male, white, older adults, veterans
82	adolescents, age 15	1,786 participants (14.6% AA)	Yes	smaller sample of AA twins may have limited power to detect racial/ethnic differences between EAs and AAs, and to examine specific factors that might contribute to racial/ethnic differences	although the majority of the sample was ascertained in the peak years for cannabis initiation and early-to-peak years for problem onset, not all participants had passed through the age of risk for the cannabis outcomes	findings may not generalize to other populations, other definitions of maltreatment, or more severe cannabis outcomes (e.g., cannabis use disorder).	
83	adolescence, mean age = 15	n = 12, 437	Yes	researchers only had access to only a half dozen dopamine-related genetic polymorphisms and it is clear that many additional genes influence alcohol use behaviors in complex ways	future work examining the joint and interactive effects of additional polymorphisms is needed prior to concluding that dopamine genes do not interact with the		

					environmental measures examined in the current study		
84	ages 21-60	109	Yes	Cannot determine causality, cross-sectional design	ALC group was more heterogeneous than the HC group	Impulsivity is a multi-faceted construct, they only used one measure of self report	
85	adults, mean age = 48	n = 489	Yes	clinical trial was conducted during the era of interferon-containing treatment regimens, which could have adversely affected linkage rate	actual negotiated HCV medication costs are unknown, a low-cost scenario using prices for current direct-acting antivirals from the Federal Supply Schedule was included in sensitivity analysis ranges		
86	adults, mean age = 49.9	n = 9865	Yes	some study samples had small coverage over some birth cohorts	different eligibility criteria for the included studies	variation associated with birth cohort could be due to the participants' age at assessment	
87	N/A	N=1,050; 44.2% male; all African American	Yes	CD and ADHD PRS were largely derived from cohorts that included a limited number of African Americans	those of African ancestry tend to have greater genetic diversity, increasing the likelihood that genetic markers that play a role in the etiology of substance use among individuals of African descent may not be observed or may be in low		

					linkage disequilibrium		
88	adult (mean 37.6)	352 cigarette smokers	Yes	use of the topography device may alter smoking puffing behaviors	Participants may not have used the device on all cigarettes smoked and the puffing behaviors might have differed between cigarettes used and not used with the device		
89	young adults (22-30 years of age)	24	Yes	Aimed to include those between the ages of 15-30 but was unable to recruit any participants under the age of 22.	Diversity in age and gender, but not in race/ethnicity. Most participants identified as non-Hispanic white	Interviews were only conducted in English	
90	adolescents, (age 11-18)	90,000 students	Yes	study explores ADV victimization, it does not examine more severe types of ADV	data on physical violence only is too small for reliable analysis	Add Health has been used to examine prior longitudinal outcomes of ADV, so more work in other datasets is needed at this time in this area of research	
91	mean age = 30.17	N=41	Yes	limited to primarily Caucasian samples	relatively small sample size		
92	N/A	N/A	Yes	differences in the in vivo apparent efficacies of heroin and morphine are very small relative to the wide range of efficacies displayed by currently available mu receptor ligands	analytical approach used in the present study to estimate tau values has acknowledged limitations that have been discussed in detail		
93	adults, (mean age 33.2 years)	44 Black participants	Yes				

94	adults, (mean age=38.58 years)	2596 unrelated individuals (44% male)	Yes	inability to model dominance and epistatic effects from genome wide loci	power to detect modest SNP-heritability estimates and genetic correlations		
95	<30 (11.5%) 30–49 (45.8%) 50+ (42.7%)	7,897; male (61%), non-Hispanic black (57%)	Yes	HIV-positive individuals in the analysis included only those who received services funded through a RWPA federal grant to the New York eligible metropolitan area	no causality due to cross-sectional data	drug use data was self-reported	use of different time frames for observing DU patterns (6–24 months) and viral load suppression (12 months)
96	mean age = 56.4	n = 1039	Yes	all subjects were of European ancestry	patient billing data was used to create phenotypes and researchers did not use natural language processing of clinical notes to identify our case cohort	could not study non-European-Americans, whose genetic diversity tends to be highest, and the mean age of the cohort suggests that we cannot necessarily generalize to younger population	
97	mean age = 49.8 years	n = 798	Yes	only patients who sought formal treatment for OUD were included	excluded patients with a history of SUD other than nicotine	smoking status was based on patient response to interview questions and not verified by a biomarker.	
98	adolescents (mean age 15.55) and adults (mean age 22.42)	n = 7228 (European 63.66%, African 20.60%, Hispanic 10.60%, East Asian	Yes	analysis is based on results from a 2010 study. replications are needed, using GWAS results from newer studies	current PRS was based on a GWAS with a European ancestry-only sample, and results may not apply to majority or	there is potentially limited statistical power in the intermediate and surrounding ages	

		5.51%); 45.89% male, 54.11% female			exclusively non-European samples		
99	adult tobacco users	19,237	Yes	Possible that PATH survey was focused primarily on tobacco use and the alcohol use outcomes lacked detail in comparison.	Possible that unmeasured traits may have confounded the association between NMR and alcohol use outcomes		
100	adults, mean age 35.4	n = 201	Yes	patients of non-Caucasian races and ethnicities were excluded from the study sample	data were cross-sectional thus a causal relationship between chronic pain or MOUD treatment and perceived support cannot be ascribed	objective indicators of social support, including social networks or family relations, were not examined to validate the patient's perception, which leaves the findings subject to patient subjectivity	
101	mean age = 39	n = 325	Yes	confounding by HCV status as participants with HIV had a significantly higher rate of HCV antibody positivity and an independent effect of HCV on methadone pharmacokinetics requires further elucidation	targeted specific genetic variants rather than conducting larger microarray studies of multiple variants, so our ability to identify haplotypes or novel variants associated with methadone pharmacokinetics is limited		
102	N/A	N =1000, stratified	Yes	genetic "inputs" that are used by these tests	candidate variants have not borne out		

		into equal groups of n =250 cases and controls each of European and African ancestry		typically comprise of "candidate gene variants" that are scored using pattern recognition software, powered with "artificial intelligence" frameworks	in unbiased genome-wide association studies (GWASs)		
103	young adults, mean age = 18.96	n = 1155 (EA (n = 750) and AA (n = 405))	Yes	sample size was modest	modest evidence of gene-environment correlation (rGE) between the PRS and community activities	analyses only include participants who had 3 consecutive observations for cannabis use, which may have impacted the representativeness of the sample	AA sample was predominantly female
104	N/A	N/A	No				
105	adults, mean age = 46.4	n = 554, African ancestry - n = 418	Yes	caution should be used when utilizing urinary NMRF/F in populations known to have faster or more variable rates of 3HC glucuronidation			
106	adults, (mean age = 46.7 years)	n = 786 (n=270 Black, n = 516 White)	Yes	lack of ability to generalize; all data was collected from participants who had volunteered to be enrolled in a smoking cessation trial in the Saint Louis metropolitan area and were motivated to quit	inclusion criteria included smoking 5 or more cigarettes per day	did not examine the potential effects of co-occurring marijuana use on exposure, intake, or intensity measures	study did not measure levels of carcinogen exposure through biomarkers such as NNAL, NNK, and polycyclic aromatic hydrocarbons (PAHs)
107	young adult (18+ years of age)	108 adult men and non-pregnant women	Yes	medication compliance = lack of data supporting riboflavin use, but subjective participant report	post-hoc analysis of only 15 participants with rs1176712:GG genotype	study arms not stratified by genotype	

				verified by pill count may not be entirely accurate			
108	adults, mean age = 50.1	533	Yes	Patients were categorized as having HCV based on HCV antibody results, and HCV RNA testing was not performed as part of this study	information on completion of fibrosis staging was not obtained, and all information on prior testing, diagnosis, and treatment was based on self-report and not substantiated by review of medical records	in 2015 we did not ask participants directly about being cured of HCV, but rather about completing treatment for HCV	
109	adulthood	1616 EA Veterans	Yes	sample in this GWAS was smaller than ideally used, so the ability to detect variants was limited.	heterogeneity from the VA medical system limited the variety of phenotypes included.	lack of information regarding drug use (route of administration, type of opioid, etc.)	predominately male sample, limited to European American (EA) patients
110	adulthood, mean age = 49.2 years	n = 1501 participants	Yes	current findings were based on secondary data analyses, and thus, are constrained by the retrospective and cross-sectional design of the original study	current study only included individuals with European ancestry.		
111	mean age 51.2	n = 150	Yes	diagnosis of MDD was determined using the ACASI, a computer interface that asks questions and records patients' answers; no structured clinical interview	participants recruited from urban settings; difficulty generalizing to the population	did not adjust p-values for multiple tests due to the nature of the present secondary analyses	
112	adults, median age = 54	738	Yes	reliance on self-reported alcohol and	CNICS protocol for assessing PRO		

				other substance use measures, where underreporting was possible and could have attenuated the magnitude of change in alcohol use present in our data	every four-to-six month at the time of a clinical visit		
113	64% of studies only included adults; others included those as young as 8 +	1,936,764	Yes	our analyses were performed in a sample of European Ancestry individuals and our results may not generalize to other populations	our prior work showed that the negative genetic correlation between PTSD-alcohol use observed in European Ancestry samples may be a positive correlation in African Ancestry samples	More research in diverse samples is essential to understand the link between PTSD and alcohol phenotypes and advancing precision medicine efforts	
114	children, (mean = 9.91)	11,875 (47.85% girls; 74.13% White)	Yes	PRS were derived from GWAS studies with relatively small sample sizes, particularly for cannabis use disorder	analyses confined to individuals in the ABCD sample who were of European genetic ancestry, to avoid potential biases		
115	adults, mean age = 41.9 years	n = 418	Yes	study sample was relatively small, limiting the possibility of discovering associations	MDD-PRS used in the study was not based on sex-specific GWAS results	association findings reported here were acquired in a sample of European ancestry	
116	early adolescence (mean = 13.53); mid/late adolescence (mean =	N = 665; European descent	Yes	sample was overrepresented by individuals who had parent(s) with AUD	accounted for a small proportion of variance		

	18.12); young adulthood (mean = 24.4)						
117	adults (aged 25-64)	n = 1006	Yes	Minority persons (i.e., Hispanic, Black, Asian) were given higher probabilities of selection than nonminority household members	the present sample had relatively few cases of some disorders, and hence, prevalence was too low to report on the reliability of some disorders	study did not examine individual items or criteria	multiple additional factors may affect reliability
118	ages 14-26, data collected at age 21	N=428 participants; 50.9% male; African Americans	Yes	although we leveraged the largest GWAS discovery results on lifetime cannabis use and cigarettes per day, these GWAS do not perfectly align with the phenotypes of past year cannabis and tobacco use	Empirical research indicates that a single liability distribution may best explain substance use initiation, frequency of use, and substance use disorder development, further supporting our approach.	Although we selected discovery results from GWAS that we believe most closely match the phenotypes under study, is it likely that individuals in the GWAS evidenced comorbid substance use behaviors and that the discovery results do not reflect specific genetic risk for cannabis or tobacco use.	
119	46±12 years of age, min = 25, max = 71	n=95, veterans	Yes	primarily male sample	there was no normal control reference group	did not include any other SNPs which may impact results	
120	Mean age = 46 years	n = 202,004	Yes	PRS are under-powered to serve as clinically useful predictors for these traits	Results are not representative of the general population because of selection biases		

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ACADEMIC VITAE
DE'JAH COATES

EDUCATION

The Pennsylvania State University, University Park, PA **August 2020 - May 2024**
Anticipated Bachelor of Science in Biobehavioral Health

Prince George's Community College (PGCC), Largo, MD **May 2020**
Associate Degree in General Studies with High Honors

HONORS

Penn State Homecoming Guide State Forward Award Recipient, 2023
Penn State Erickson Grant Recipient, 2023
Penn State Schreyer's Honors College Scholar, 2022 - Present
Penn State Millennium Scholars Program Scholarship Recipient, 2020 - Present

EXPERIENCE

Pennsylvania State University, University Park, PA **December 2021 - Present**
Morbidity, Mortality and Demography Lab, Honor's Research Assistant

- Completed a scoping review of the literature on genetics/genotypes and their influence in substance use, health behaviors and health from the journal *Drug and Alcohol Dependence*, one of the major outlets in the discipline. Applied the PRISMA methodology and analyzed studies to produce a comprehensive analysis of the knowledge produced between 2000 and 2023.

Behavioral Neurogenetics Laboratory, Undergraduate Research Assistant

- Reviewed previous lab studies and results relating to the role of chronic variable social stress on adolescent mice and morphine dependency in adulthood, using methods of gene expression measurement and electrophysiology. Applied findings to develop a design for replication of these experiments using mild physical stressors and examine opioid sensitization in laboratory mice.

National Institute on Drug Abuse, Baltimore, MD **June 2022 - August 2022**
Recruitment and Training to Unlock Research Potential in Science, Aponte Lab Research Intern

- Analyzed results of electrophysiological techniques using MATLAB and ImageJ/Fiji to determine neuronal activity via calcium imaging in high-fat-diet in mice to study the role of feeding regulation hormones, CCK, Ghrelin, and neuropeptide Y in binge-eating disorders.

University of Minnesota - Twin Cities, Minneapolis, MN **May 2021 - August 2021**
Life Science Summer Undergraduate Research Program (LSSURP), Gomez-Pastor Lab Research Intern

- Executed successful mutagenesis and transfection experiments on Q111 HD mouse striatal cell cultures to examine the role of alpha-synuclein and CK2a' protein kinase in Huntington's disease (HD). Presented on the overexpression of a-syn and the inverse effects on the expression of many synaptic genes in HD models.

PRESENTATIONS

"Underlying mechanisms of diet-induced obesity in mice". National Institutes of Health Intramural Research Program Summer Poster Day, Bethesda, MD, August 2022.

"Alpha-synuclein abundance affects synaptic dysregulation in Huntington's Disease." University of Minnesota Summer Undergraduate Research Symposium, Minneapolis MN, August 2021.

PUBLICATIONS

Yu, D., Zarate, N., White, A. *et al.,* including **D. Coates**. CK2 alpha prime and alpha-synuclein pathogenic functional interaction mediates synaptic dysregulation in Huntington's disease. *Acta Neuropathol Commun* 10, 89 (2022). https://doi.org/10.1186/s40478-022-01397-6

COMMUNITY INVOLVEMENT

- **Pennsylvania State University National Pan-Hellenic Council** - *President, April 2023 - April 2024*
- **Penn State Health Promotion & Wellness Intern** - *Health Equity Team Lead, HealthWorks, April 2023 - April 2024*
- **Delta Sigma Theta Sorority, Inc., Epsilon Gamma Chapter** - *Recording Secretary, December 2022 - April 2024*
- **Millennium Scholars Program Mentor** - *Mentor, August 2022 - April 2024*
- **Diversity and Inclusion Student Association (DISA) in the College of Health and Human Development** - *Vice President, April 2022 - April 2023*
- **Penn State Student Black Caucus** - *University Park Undergraduate Association (UPUA) Representative, March 2022 - March 2023*