The Epidemiology of Alcohol and Drug Disorders

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Contents

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What is Epidemiology?

The field of epidemiology involves investigation of the distribution and determinants of health conditions in populations or population subgroups. Epidemiological investigations fall under two common domains: descriptive and analytic. Descriptive epidemiologic studies provide estimates of the incidence and prevalence of illnesses or health behaviors. Incidence refers to the proportion of new cases of a particular health outcome during a specific period of time in a specific at-risk population (i.e., among individuals free of the outcome at the beginning of the time period). Prevalence refers to the proportion of a group or population affected with a health condition at a particular point in time. This includes new cases as well as chronic cases that began earlier and continued into the period of observation. Analytic epidemiologic studies focus on identifying causes/risk factors (e.g., genetic variants, contextual circumstances) of illness, often done through retrospective comparison of cases with non-cases or prospective study of disease development among individuals exposed versus unexposed to a particular hypothesized causal factor.

This chapter covers the epidemiology of alcohol and drug abuse and dependence (referred to together as "substance use disorders"). From an epidemiologic standpoint, substance use disorders have common as well as unique characteristics. This chapter identifies common characteristics of the epidemiology of alcohol and drug use disorders, and highlights

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some important characteristics unique to specific substances.

Substance Use in the United States: A Historical Overview

Alcohol Consumption

The use of substances to alter mood states has been a part of civilization from pre-historic through modern time periods. Archeological records document the conversion of sugar into fermented beverages for recreational use, as part of religious ceremonies, and as an analgesic or disinfectant as early at 10,000 B.C. [1, 188]. Alcohol remains incorporated into the fabric of many cultures for a variety of uses, including social and recreational use, as a part of religious ceremonies, secular festivities, and as a normative aspect of daily life. Further, moderate consumption is associated with health and longevity, and is considered to be protective against several adverse health outcomes including cardiovascular disease [13].

Long-term historical information on United States alcohol consumption is available through per-capita alcohol consumption statistics derived from sales records. These records show drinking levels in the United States varied greatly over time from the early days of the United States to the twenty first century [169, 172]. Per-capita consumption levels ranged from extraordinarily high levels during the United States colonial period (from an estimated 5.8 gallons per year per capita in 1790 to 7.1 gallons in 1830) to very low levels before and during Prohibition (from an estimated 1.96 gallons in 1916 to 0.97 gallons in 1934). Prohibition refers to the time period during which the United States prohibited the manufacture, sale, and transportation alcoholic beverages were prohibited by the 18th Amendment to the Unites States Constitution. This period began in 1920, and ended in 1933 with the repeal of the 18th Amendment by the 21st Amendment. From 1935 until 1982, shown in Fig. 1, per-capita alcohol consumption increased steadily to a peak of nearly 2.8 gallons of ethanol per year in 1982 [169]. Since then, consumption has declined, leveling off at about 2.2 gallons of ethanol per year in 1993, and

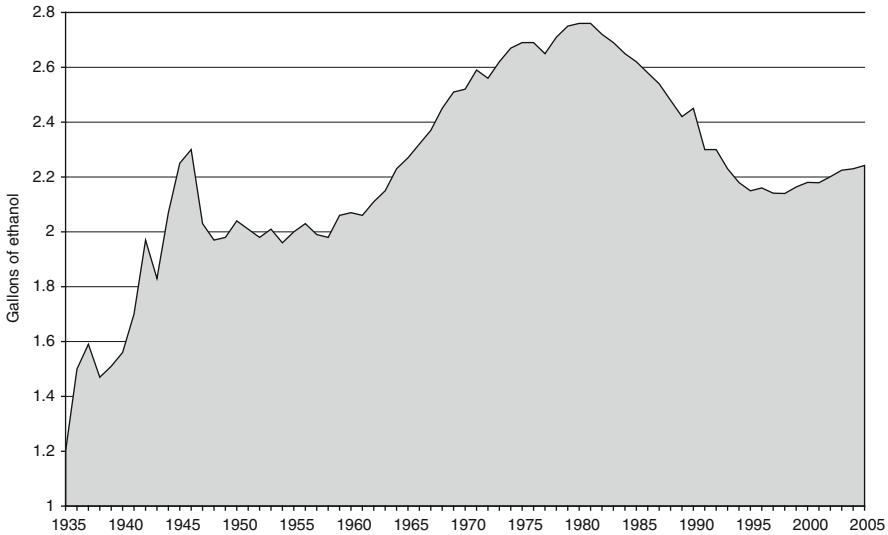

Fig. 1 Total per-capita ethanol consumption, United States, 1935–2005. Source: Lakins NE, LaVallee RA, Williams GD, Yi H (2007) Surveillance report #82: apparent per capita alcohol consumption: national, state, and regional trends, 1977–2005. NIAAA, Division of Biometry and Epidemiology, Alcohol Epidemiologic Data System, Rockville, MD, August 2007

remaining at around that level until 2005, with a slight increase from 1999 to 2005. These data are generally consistent with liver cirrhosis mortality statistics, which show similar variations over time [287].

Worldwide, alcohol consumption patterns vary considerably. Consumption is lowest in predominately Muslim countries (e.g., individuals in Afghanistan and Pakistan consume 0.03 and 0.31 l pure alcohol per capita, respectively) and eastern Mediterranean countries, and highest in eastern European countries (e.g., individual in Ukraine and the Russian Federation consume 15.58 and 15.23 l pure alcohol per capita, respectively) and western European countries such as France, Germany, and the United Kingdom [285].

Alcohol consumption is also heterogeneous within countries. For example, about one-third of United States adults do not drink, although per-capita consumption is 9.3 l [216, 224]. Abstainers are rare In Eastern Europe (including Russia and Ukraine), where per-capita consumption, 13.9 l, is the highest in the world [216]. After immigration, immigrants tend to retain the drinking levels of their country of origin rather changing to the patterns of their new country, for example, Mexican immigrants in the United States [89] and Russian immigrants in Israel [107, 214].

Drug Use

Drugs such as cannabis, opium, and cocaine have been cultivated and used medicinally as well as recreationally for centuries. Opium poppies are believed to have been first grown in the region near modern-day Iraq as early as 3400 B.C. Opium was used primarily as an analgesic and anesthetic, but medical use did not become widespread until the development of the hypodermic needle in the early 1800s [200]. Historical analysis also indicates that marijuana was smoked recreationally and medically in ancient China as early as 2737 B.C. [199]. In South America, societies have grown and consumed coca, the plant grown to create cocaine, for centuries. The most common mode of administration is to chew the leaves of the coca plant, or to mix the leaves into a tea [252]. In the twentieth century, innovations in pharmacological knowledge led to the development of synthetic drugs such as lysergic acid diethylamide, categorized as a hallucinogen, and methylenedioxymethamphetamine (or "ecstasy"), categorized as an amphetamine.

In Western countries prior to the 1960s, drug use was rare and the few studies that addressed prevalence focused on heroin, with widely varying results [56, 90, 243]. Morphine is believed to have been prescribed often in the nineteenth and early twentieth centuries mainly as a cough suppressant to ease the suffering of individuals with tuberculosis [199], although no data are available to empirically estimate incidence and prevalence. During the Civil War, it is believed that more than 400,000 soldiers became dependent on morphine, as it was liberally prescribed for pain associated battle wounds [199]. More systematic surveys of United States drug use began in the 1960s. A series of national household surveys on drug use conducted by the National Institute on Drug Abuse and later by the Substance Abuse and Mental Health Services Administration showed that illicit drug use, especially marijuana, increased greatly after the late 1960s (Fig. 2). Heroin use also increased in the late 1960s, when the profile of users changed from "bohemians" to inner-city, unemployed males. Yearly surveys of United States youth [140] since 1975 indicate that ~50% of 12th-grade students have used an illicit drug, with a high of 66% in 1982, a low rate of 41% in 1992, and 51% in 2004. Since 1975, over 80% of students felt that marijuana was easily available, ranging from 82.7% in 1992 to 90.4% in 1998.

Substance Use in the United States: A Public Health Problem

While alcohol and drug use is common both in the United States and in many countries worldwide, excess alcohol consumption is estimated to be the 3rd largest cause of United States

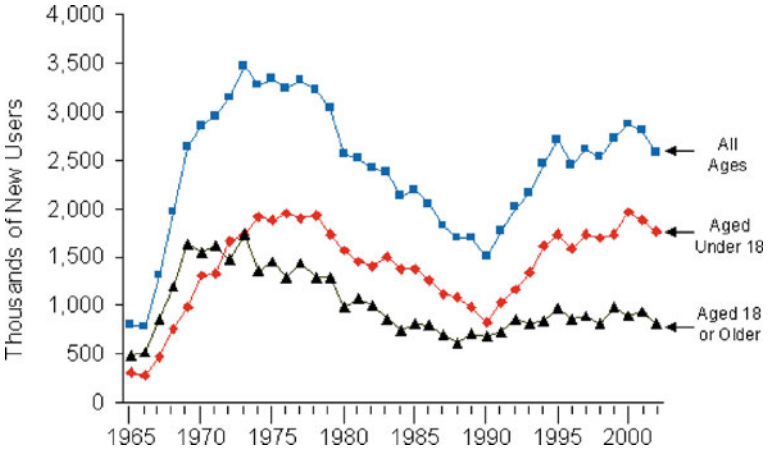

Fig. 2 New users of cannabis in the United States, 1965–2002. Source: Substance Abuse and Mental Health Services Administration (2004). Results from the 2003 National Survey on Drug Use and Health: National Findings

preventable mortality [197] and the 5th largest cause of preventable disability worldwide [66]. Excess substance use and substance use disorders are associated with a broad range of adverse outcomes including but not limited to accidents and traffic fatalities [126], domestic violence [25], fetal alcohol syndrome and other pre- and perinatal insults [211, 246], neuropsychological impairment [11], poor medication adherence (e.g., HIV) [229], economic costs and lost productivity [98], psychiatric comorbidity [21, 114], and functional disability [114]. Thus, prevention and intervention of excess substance use is an important public health priority.

When Does Use Become Pathological? Substance Abuse and Dependence

The two major nomenclatures, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, define psychiatric disorders within a common framework for individuals and groups with different training, experience, and interests. Users include medically and behaviorally trained clinicians, neuroscientists, geneticists, investigators conducting clinical trials, epidemiologists, policy makers, insurance companies and others. Both the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the research version of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision enable diverse groups to arrive at common definitions of disorders by providing specific, generally observable criteria for each disorder. For substance use disorders, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision provide diagnostic criteria for two disorders, dependence and abuse (shown in Tables 1 and 2). The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision also provide symptoms for diagnosing substance-specific intoxication and withdrawal syndromes, and methods for diagnosing substance-induced psychiatric disorders. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition was developed in the United States by the American Psychiatric Association and is used in the United States and internationally in research studies. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision was developed by the World

Table 1 Dependence criteria: International statistical classification of diseases and related health problems, 10th revision (ICD-10) and *diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV)

Substance	ICD-10	DSM-IV
All substances	*Three* or more of the following six symptoms occurring together for *at least 1 month, or* if less than 1 month, occurring together *repeatedly within a 12-month period*: 1. Tolerance: need for significantly increased amounts of alcohol to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount of alcohol. 2. A physiological withdrawal state of the characteristic withdrawal syndrome for alcohol, or use of alcohol (or closely related substance) to relieve or avoid symptoms. 3. Difficulties in controlling drinking in terms of onset, termination, or levels of use: drinking in larger amounts or over a longer period than intended; or a persistent desire or unsuccessful efforts to reduce or control drinking. 4. Important alternative pleasures or interests given up or reduced because of drinking; *or* a great deal of time spent in activities necessary to obtain or use alcohol or to recover from its effects. 5. Persisting with drinking despite clear evidence and knowledge of harmful physical or psychological consequences 6. A strong desire or sense of compulsion to drink.	A maladaptive pattern of drinking, leading to clinically significant impairment or distress as manifested by *three* or more of the following seven symptoms occurring *in the same 12-month period*: 1. Tolerance: need for markedly increased amounts of alcohol to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of alcohol. 2. The characteristic withdrawal syndrome for alcohol (or a closely related substance) or drinking to relieve or avoid withdrawal symptoms. 3. Persistent desire or one or more unsuccessful efforts to cut down or control drinking. 4. Drinking in larger amounts or over a longer period than the person intended. 5. Important social, occupational, or recreational activities given up or reduced because of drinking. 6. A great deal of time spent in activities necessary to obtain, to use or to recover from the effects of drinking. 7. Continued drinking despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by drinking.

Health Organization and is used internationally, mainly for clinical purposes and governmental reporting.

Substance Disorders in the Diagnostic and Statistical Manual of Mental Disorders

The substance dependence criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, shown in Table 1, are based on the alcohol dependence syndrome [62], which was generalized to drugs in 1981 [286]. Dependence was considered a combination of physiological and psychological processes leading to increasingly impaired control over substance use in the face of negative consequences. Dependence was one "axis" of substance problems, and the consequences of heavy use (social, legal, medical problems, hazardous use) a different axis of substance problems. This bi-axial concept [61] led to the distinction between abuse criteria (social, role, legal problems or hazardous use, most commonly driving while intoxicated) and dependence (tolerance, withdrawal, numerous indicators of impaired control over use).

The focus on *dependence* is based on its centrality in research and on its psychometric properties. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined dependence and International Statistical Classification of Diseases and Related Health Problems, 10th Revision—defined dependence have good to excellent reliability across samples and instruments [24, 26, 83, 99, 101, 108, 265], with few exceptions (rare substances; hallucinogens). Dependence validity has also been shown to be good via several study designs. These include: multi-method comparisons [40, 80, 108, 115,

Table 2 Abuse/harmful use criteria: international statistical classification of diseases and related health problems, 10th revision (ICD-10) and *diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV)

Substance	ICD-10	DSM-IV
All substances	**A**: Clear evidence that alcohol use contributed to physical or psychological harm, which may lead to disability/adverse consequences. **B**: The nature of harm should be clearly identifiable (and specified). **C**: The pattern of use has persisted for at least 1 month or has occurred repeatedly within a 12-month period. **D**: Symptoms do not meet criteria for any other mental or behavioral disorder related to alcohol in the same time period (except for acute intoxication).	**A:** Criteria for alcohol dependence have never been met. **B:** A maladaptive pattern of drinking, leading to clinically significant impairment or distress as manifested by at least *one* of the following four symptoms occurring within a 12-month period: 1. Recurrent use of alcohol resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household). 2. Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol use). 3. Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct). 4. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication).

213, 226, 231]; longitudinal studies [88, 100, 101, 109, 233, 235]; latent variable analysis [16, 97, 201], and construct validation [105, 113]. Animal models of a syndrome of cocaine dependence symptoms (as distinct from use patterns) [50, 222, 266] lend credence to the dependence syndrome not only as a cross-cultural phenomenon, as suggested by a World Health Organization study [40, 101, 213], but a cross-species phenomenon as well.

Substance *abuse* is a different case. Contrary to clinical assumptions, abuse does not necessarily lead to dependence [88, 100, 109, 116, 233, 235]. Further, not all cases of alcohol or drug dependence have abuse symptoms [110, 111]. Dependence is more familial than abuse [103, 109]. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol abuse is most often diagnosed in the general population based on one symptom, driving while intoxicated [104, 106, 156]; preliminary analyses of national data show this is also the case for drug abuse. A *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined diagnosis of abuse may thus depend on the availability of a car, while dependence is a heritable, complex condition.

Various psychometric analyses have been conducted to examine the validity of the Edwards and Gross taxonomy of two distinct, correlated factors for substance abuse and dependence criteria. Confirmatory factor analysis on the alcohol abuse and dependence items has provided mixed evidence; several studies show that a two-factor model best describes abuse and dependence items [84, 97, 201, 202], while several others found evidence of similar model fit for one- and two-factor models, preferring the

one-factor model on the basis of parsimony and high factor correlations [187, 212]. Factor analyses of cannabis abuse and dependence items have generally found support for a one-factor model or similar fit of one- and two-factor models [3, 73, 187, 203, 257], although results from a general population survey support a two-factor model [16]. Taken together, these studies show some support for combining abuse and dependence albeit with some evidence to the contrary. Differences across study may also have occurred due to characteristics of the populations studied (e.g., general population versus community sample, adults versus adolescents). A current unresolved issue for those preferring a single substance use disorder that combines abuse and dependence criteria is a valid threshold for differentiating between cases and non-cases. This issue will need to be resolved if the criteria are to be combined, for example, in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.

Substance Disorders: A Categorical or Dimensional Trait?

Recent psychometric analyses of the substance abuse and dependence criteria have suggested that these disorders are not categorical entities; instead, evidence supports an underlying continuum of alcohol severity across a variety of samples and populations [112, 142, 164, 185, 212, 228]. Such information may be critical when statistical power is limited, as it often is in studies of gene–gene or gene–environment interaction. If *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol dependence in categorical form is psychometrically sound (i.e., reliable and valid) but dichotomizes an inherently dimensional condition, then converting its elements to a dimensional measure may produce a more informative phenotype for etiologic studies [112]. Future versions of the diagnostic nomenclature will likely incorporate a dimensional form of substance dependence [122], but further psychometric and etiologic work validating dimensional forms of substance disorders remains necessary.

Descriptive Epidemiology: The Incidence and Prevalence of Substance Disorders

Prevalence and Incidence of Substance Disorders

The most comprehensive epidemiologic United States information on the incidence and prevalence of alcohol disorders comes from the National Epidemiologic Survey on Alcohol and Related Conditions, a longitudinal survey of 43,093 respondents aged 18 years and older conducted in 2001–2002 [81, 82, 85] with a 3-year follow-up of 34,653 respondents [82]. The diagnostic interview was the Alcohol Use Disorder and Associated Disabilities Interview Schedule—*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition Version [82], a structured interview for non-clinicians with high reliability and validity for substance use disorders [26, 83, 108, 227, 265].

In the National Epidemiologic Survey on Alcohol and Related Conditions, the prevalence of current (past 12 months) alcohol abuse and dependence was 4.7 and 3.8%, respectively, for a total prevalence of 8.5% for any current alcohol use disorder [114]. The prevalence of lifetime alcohol abuse and dependence was 17.8 and 12.5%, respectively, for a total prevalence of 30.3% for any lifetime alcohol use disorder [114]. Current and lifetime alcohol disorders are more prevalent in men (current: 12.4%, lifetime: 42.0%) than in women (current: 4.9%, lifetime: 19.5%). Compared with individuals of White race/ethnicity, among whom the current and lifetime prevalence of alcohol disorders was 8.9 and 34.1%, respectively, Blacks, Hispanics, and Asians have a lower prevalence of current and lifetime alcohol disorders (6.9 and 20.6% for current and lifetime alcohol disorders among

Blacks, 7.9 and 21.0% Hispanics, and 4.5 and 11.6% among Asians. Alcohol disorder prevalence is inversely related to age; those in younger age groups are most likely to have an alcohol disorder, with mean ages at onset of alcohol abuse and dependence at 22.5 and 21.9, respectively [114]. The incidence of alcohol dependence was 1.66 per 100 person-years [85], meaning 1.66 cases per year of alcohol dependence for every 100 individuals without alcohol dependence at the beginning of that year. Incidence of alcohol abuse was slightly lower at 1.03 per 100 person-years [85]. In general, predictors of incidence were similar to predictors of prevalence.

Drug disorders were substantially less common than alcohol disorders. The prevalence of current (past 12 months) drug abuse and dependence was 1.4% and 0.6%, respectively, for a total prevalence of 2% for any current drug use disorder [227]. The prevalence of lifetime drug abuse and dependence was 7.7 and 2.6%, respectively, for a total prevalence of 10.3% for any lifetime drug use disorder [227]. Current and lifetime drug disorders are more prevalent in men (current: 2.8%, lifetime: 13.8%) than in women (current: 1.2%, lifetime: 7.1%). Drug disorder prevalence is inversely related to age; those in younger age groups are most likely to have a drug disorder, with mean ages at onset of drug abuse and dependence at 19 years. There is no consistent trend by race for drug disorders [227]. In the National Epidemiologic Survey on Alcohol and Related Conditions, incidence of drug dependence was estimated at 0.32 per 100 person-years of observation [85]; incidence of drug abuse was slightly lower at 0.28 per 100 person-years. In general, predictors of incidence were similar to predictors of prevalence.

The Course of Substance Disorders

Initiation of alcohol consumption and drug use often occurs during adolescence. Onset of alcohol abuse and dependence is most likely among individuals aged 18–29, although 15% of alcohol dependence cases begin before age 18 [127]. Often, substance disorders are not lifelong conditions. Indeed, a high rate of recovery has been documented in general population samples, even among individuals who have never sought treatment. Studies of alcohol disorders in the general population also show that a high proportion of recovered individuals return to moderate drinking as opposed to abstinence [47, 277]. Data from the National Epidemiologic Survey on Alcohol and Related Conditions indicated that approximately 75% of individuals diagnosed with alcohol dependence at some point in the past did not have a current (i.e., past year) diagnosis, but that only about 20% of these individuals were abstinent from alcohol [47]. However, prospective follow-up of this sample has indicated that low-risk drinking represents a risk factor for relapse to an alcohol disorder compared with abstinence [45]. Longer term prospective follow-up of this general population sample will help to clarify the role of alcohol consumption in recovery from disorder.

The transition to adulthood represents a key developmental phase in which alcohol disorders often remit, in a process termed “maturing out” [8, 46]. Major predictors of recovery include key lifestyle components, such as employment, marriage, and childbirth. Whether or not these factors have a causal influence on recovery or reflect common factors underlying the positive lifestyle components and the recovery remains unknown.

Despite substantial progress in the development of treatments for alcohol and drug disorders, only about one-fifth of those individuals with an alcohol disorder [34, 114] and one-sixth of individuals with a drug disorder [35] seek treatment for the condition during their lifetime. Further, the delay from onset of disorder to treatment is typically 8–10 years [276]. Finally, in contrast to sharp increases in treatment utilization for disorders such as depression between 1990 and 2003 [153], a corresponding increase in the proportion of individuals seeking treatment for an alcohol and drug disorders did not occur during this period [114].

The path from first use to dependence to treatment also differs by gender. Women who

use alcohol and drugs often start using later than men, have a faster progression from first use to dependence, and enter treatment sooner than men given equal ages of dependence onset [209, 215], although no such differences have been observed for crack-cocaine users [55, 171]. This phenomenon has been termed "telescoping".

Evidence is accumulating that these well-documented gender differences in the course of alcohol disorders are converging. Studies of adolescent alcohol use have consistently shown a convergence in rates of alcohol and drug use initiation in younger birth cohorts, especially those born after World War II [139, 141]. Further, several genetically informative samples have researched gender differences in *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol and drug disorders over time, unanimously finding support for such a convergence [128, 220]. Similarly, large, representative cross-sectional studies in the United States support gender convergence in rates of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol abuse and dependence [92, 155]. Finally, evidence indicates that the traditional "telescoping" phenomenon whereby women exhibit later onset of drug use and disorder but earlier treatment and shorter course may be diminishing, as women are more closely approximating men in both onset and course of disorder [129]. Searches into the causes of these shifts are ongoing, but this evidence indicates increased social acceptability of alcohol use by women in younger generations [91].

Analytic Epidemiology: The Etiology of Substance Disorders

Substance use disorders have a complex etiology involving genetic and environmental factors. These occur along a continuum ranging from the macro level consisting of broad social influences, to the micro level, consisting of molecular-level influences. These can be thought of as external to internal levels (Fig. 3). In the remainder of this chapter, we address these levels in turn. We begin with macro/external factors, including societal availability and desirability of the substances, geographic and temporal differences, pricing, laws, and advertising. We next consider externally imposed stress. Intermediate-level factors include religiosity, parental and peer social influences. Moving increasingly toward the micro and internal levels, we consider cognitive and personality variables, subjective responses to substances, and specific risk as well as protective genes. We conclude by discussing gene-by-environment interaction, addressing the idea that since etiologic influences work at various levels, a factor at any level may emerge more clearly if other levels are considered conjointly.

Availability—Temporal and Geographical

Political Events

Political events, both local and global, influence the availability of substances and thus the risk

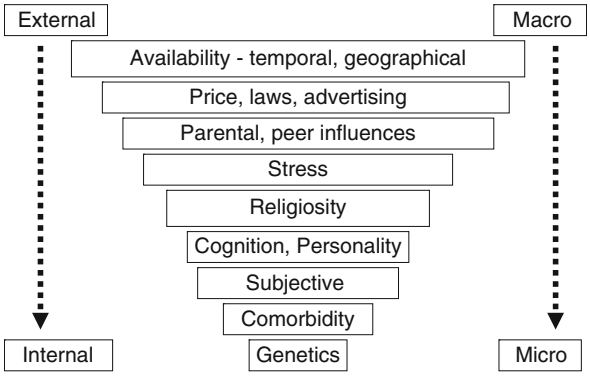

Fig. 3 Factors affecting substance use and substance use disorders

of substance use and dependence. In 2004, for example, religiously motivated attacks on alcohol retailers in Iraq (*BBC World News*, July 22, 2004) reduced the availability of alcohol locally for that region. After the Taliban government fell in Afghanistan in 2001, heroin production in Afghanistan increased greatly [165], coinciding with increased heroin use among American teenagers [255]. Political instability in South American countries such as Bolivia and Colombia, especially in the 1970s, influenced the production of cocaine and increased the availability of cocaine in the United States [251]. Thus, political events at a great geographic distance may influence local substance use availability and patterns of use.

Outlet Density

Counties, cities or states with higher density of alcohol outlets (places were alcohol is sold) have higher alcohol consumption and higher rates of alcohol-related problems, including hospital admissions, pedestrian injury collisions, and crashes and crash fatalities [33, 237, 256, 261, 262]. Ecologic and multilevel analysis controlling for individual level factors indicates that outlet density is related to higher mean group rates of consumption and drinking norms scores and to driving after drinking [93, 237]. Community-based interventions to limit access to alcohol by reducing the density of outlets have been shown to reduce alcohol-related traffic injury and self-reported consumption [130]. While information regarding outlet ("dealer") density is unavailable for drugs, the vigorous efforts of parents, schools, and law enforcement agencies to keep drug dealers away from schools are consistent with the same idea.

Pricing, Laws, and Advertising

Pricing

Alcohol taxation is the major determinant of state variation in the price of alcohol, and is thus a government intervention. An inverse relationship exists between state-level price of alcohol and per-capita consumption or adverse consequences of drinking [30]. Further, higher state-level beer tax is associated with lower prevalence of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition—defined alcohol dependence [123]. Outside the United States, cutting the tax on spirits has been followed by increased per-capita alcohol consumption [120, 223].

Laws and Law Enforcement: Alcohol

Laws and their enforcement also affect consumption patterns. In the United States, the 18th Amendment to the Constitution outlawed the manufacture, transport, and sale of alcohol from 1920 to 1933. Figure 1 shows that in 1935, per-capita ethanol consumption was very low, but increased steadily afterwards, consistent with cirrhosis mortality rates from the same period [171, 287]. Thus, the 18th Amendment achieved its purpose, but was repealed because it was unacceptable to the public. Similar events occurred in the former Soviet Union, an area of very high per-capita alcohol consumption [285]. In the mid-1980s, the government attempted to restrict consumption. The policies were successful in reducing consumption, but so unpopular that they contributed to the downfall of the government and were eventually reversed [240].

More recently in the United States, enforcement of laws related to drinking and driving has been shown to be an important deterrent to alcohol-related crashes and fatalities. These include driver's license suspensions [268], and lowering the maximum legal blood alcohol concentration among drivers [69, 259, 269]. In addition, stricter driving-under-the-influence laws and their enforcement are consistently related to decreased hazardous use [182] and alcohol-related traffic fatalities [6, 268].

Minimum-age drinking laws influence the availability and acceptability of consumption among young people. Laws vary considerably by country both in scope and in minimum age [285]. For example, the minimum consumption

age in the United States is 21, while in Cyprus it is 12. Israel did not have a minimum legal drinking age until 2004, but public concern about increased risky drinking among young adults led to the establishment of a national minimum drinking age (18 years) at that time [248]. Some countries have separate age restrictions for consumption and purchase. For example, in Greece the minimum consumption age is 14 while the minimum purchase age is 17. In Italy, there is no age restriction on consumption in private, but a minimum age requirement of 16 to drink in public.

Minimum drinking age laws have a positive effect on community health as well as the health and safety of adolescents. Research in the United States and other developed countries has indicated that minimum drinking age laws reduce traffic crash and fatality rates [68, 241, 268, 271]; positive effects among adolescents include reducing in alcohol consumption and high risk drinking [206]. Additionally, several studies have documented an association between minimum drinking age laws and a reduction in youth suicide [15, 21].

State Distribution Policies

In the United States, states differ in the ways they control availability of alcohol. Some states exert more control through operation of state alcoholic beverage sales, while others exert less control through the licensing of alcohol outlets. This difference impacts sales and consumption patterns [270]. Compared with "wet" counties, "dry" counties, where alcohol is not sold, have lower rates of alcohol-related accidents, driving-under-the-influence arrests, and cirrhosis mortality [283]. International studies corroborate these findings; in Norway, stringent alcohol regulations, such as mandatory closing on Saturdays, led to lower detoxification admissions [223].

Grass-Roots Efforts

Mothers Against Drunk Driving was started in 1980 by a group of women after a teenage girl was killed by a repeat-offense drunk driver. Mothers Against Drunk Driving, a very active organization, national since the early 1980s, has been highly effective in influencing state legislation pertaining to intoxicated driving, such as increasing the minimum drinking age from 18 to 21, and enforcement of maximum-blood-alcohol-level laws among drivers [95]. In particular, a highly publicized media campaign called "Rate the State" in which states were graded A through D on driving-under-the-influence countermeasures, put pressure on legislators to increase the stringency of these laws, shown as an effective strategy in reducing alcohol-impaired driving [242, 267].

Alcohol Marketing and Advertising

Product development and marketing aim to increase sales and consumption [29]. Alcohol companies allocate substantial resources to researching consumer preferences, developing new products and promoting them [138]. For example, the alcohol beverage industry spent 696 million dollars on magazine advertising alone between 1997 and 2001, largely targeted to adolescents [74]. The alcohol industry does not publish the results of its marketing research, and resources necessary for definitive public health studies of advertising and other marketing effects are limited by comparison.

Public health concerns often focus on marketing that targets adolescents [28, 39]. Existing data from longitudinal studies show associations between late childhood-early adolescent exposure to advertising and subsequent drinking initiation and frequency [37, 64, 249]. Cross-sectional studies also show associations of various marketing and advertising strategies with positive attitudes about drinking and drinking frequency [71, 167]. Further, an imaging study of adolescent response to alcohol advertising indicated greater brain activation in areas linked to reward and desire among adolescents with alcohol use disorders than infrequent drinkers [254], suggesting that advertisements are especially salient to vulnerable adolescents.

Laws and Law Enforcement: Drugs

A literature on government efforts to reduce drug use by reducing availability is inconsistent. Some studies suggest the strategies are ineffective [17, 279, 284], while others find supply reductions efficacious [48, 278]. Reducing the supply of specific drugs can have unintended consequences, including increases in other substances [260]. Data from United States college studies, however, indicate that increased restrictions on alcohol use does not increase marijuana use, as has been hypothesized, but instead serves to decrease both alcohol and marijuana use [281]. Thus, the evidence is inconsistent on the efficacy of government attempts to limit drug use by reducing supply.

Parental and Peer Influences

Parental Modeling of Substance Use

Twin studies indicate that up to half the liability to alcohol dependence is environmental [225]. Parental modeling has been proposed as one such environmental factor affecting subsequent substance use in their children [65]. Adoption studies do not support this, however, since rates of alcoholism in adoptive children of alcoholics are not elevated [132]. One etiologic model with empirical support from twin studies posits that influential factors for substance use and the progression to dependence change over time; environmental and social factors mediate the initiation and use of substances in childhood and adolescence, while genetic factors become more influential in the adult substance use and dependence [151].

Parenting Practices

Poor parental monitoring increases association with substance-abusing peers [117], a risk factor for alcohol misuse (see below, peer influences). Harsh, inconsistent parenting predicts earlier initiation of alcohol use, conduct problems and poor regulatory competencies [166, 217]. On the other hand, warm yet authoritative parenting styles protect adolescents from alcohol problems [207].

Peers

Peer influence is a strong predictor of adolescent drug and alcohol use and problems [143, 250, 272]. Twin studies show that shared environmental influences such as peers have a significant effect on initiation of alcohol and any drug use [157, 219]. Two models have been proposed to explain peer influence on adolescent substance use, social selection, and socialization [144]. The social selection theory proposes that young adolescents selectively "mate" with friends; those children who display deviant behavior as children will be prone to choose deviant friendships in adolescence [70]. This can lead to initiation of drug use (especially marijuana use) and may be a factor in the transition to "heavier" drugs. It has been further proposed that an underlying trait such as sensation seeking (see below) influences both the selection of peers and substance use [53]. In contrast, the socialization theory proposes that adolescents can be influenced to use substances by peers in their environment [49] via modeling, offers, development of expectancies, and social norms [18, 236]. Substance use by older siblings is also associated with individual substance use [23, 75, 136, 190]. Studies that could examine these various environmental effects while controlling for genetic influences are needed to resolve the social selection/causation debate.

Peers may also be protective. Some United States ethnic/immigrant groups use substances less than the norm [89]. Adolescents from these groups with ethnically homogeneous peers encounter less pressure to use substances [22].

Stress

Drug disorders are often preceded and accompanied by disruptive behavior and conduct

problems [168] that have a shared genetic vulnerability with drug disorders [149]. These behaviors evoke negative reactions from the environment, resulting in stressful life events that are not always independent of the individuals, making a causal direction between stress and disease onset difficult to discern. In animal studies where stress can be experimentally applied, cause and effect are clearer, as is also the case in studies of early stressful experiences in humans that antedate the onset of substance use disorders.

Animal Models

In animal studies, the timing of stress relative to normal development can be experimentally manipulated. In adult animals, substance use increases after physical stressors [76, 210] and social stressors [44, 85, 96, 194].

Early life stressors also contribute to drug-using behaviors in animals. Neonatally isolated rats are more likely to acquire stimulant self-administration behaviors [134, 160, 179] and show higher dopamine levels in response to cocaine than handled rats, suggesting that early stress leads to greater cocaine reward [20, 161]. Early-life rearing stressors predict ethanol seeking in primates [10]. Isolated rearing led to increased drinking of morphine solution under various conditions [5, 184]. Recently developed animal models of Δ9-tetrahydrocannabinol self-administration [19] may allow similar studies for cannabis.

Early Stressors and Drug Use in Humans

Childhood stressors, including parental separation, neglect and abuse (physical and sexual) are associated with later substance use, problems and dependence [54, 150, 152]. However, most studies failed to control for parental history of substance abuse, a potential confounder given that substance abuse is associated with poor parenting [174]. One informative study showed that among adolescents with a substance-abusing parent, strong family cohesion (the opposite of neglect) protected against drug problems [133]. Twin studies allow the study of environmental stressors while controlling for genetic influences and have shown that childhood sexual abuse is an environmental risk factor for substance use disorders [147, 204]. Effects of other childhood adversities (e.g., neglect, physical and emotional abuse) have not been examined in twin studies.

Religiosity

Religiosity has been called "one of the more important environmental factors that affect the risk for substance use and dependence" [148]. An inverse relationship between religiosity and drinking is cross-cultural [4, 7, 208]. Longitudinal studies of adolescents, college and professional students show that religiosity protects against later heavy drinking [9, 183]. Religiosity is strongly correlated within twin pairs due to shared environmental effects [148, 158, 263]. Heritability of drinking differs between religious and non-religious twins, an example of gene-environment interaction [159]. In twins studied longitudinally [148], religiosity predicted later drinking more than drinking predicted later religiosity, suggesting that religiosity is more likely to influence drinking than the reverse. These studies indicate that religiosity is largely environmental and protects against alcohol use disorders. Religiosity also protects against drug disorders [31, 198], although this literature is less extensive.

Cognition, Personality

Substance Expectancies and Motivations

Positive substance expectancies constitute an important risk factor for the development of alcohol dependence [78, 238]. For example, alcohol expectancies are considered the beliefs that drinking alcohol will result in decreased

negative emotions or enhanced positive emotions [77, 245]. These expectancies can be derived from parents and peers, and are believed to be environmentally influenced rather than genetically influenced [244]. Motivations for drinking often fall under four main domains: (1) drinking to obtain social rewards or enhance social interactions; (2) drinking to enhance positive mood; (3) drinking to reduce negative mood, and (4) drinking to avoid social rejection and conform to social norms. While individuals with alcohol disorders often rate all motivations highly, reduction of negative affect and enhancement of positive affect have been prospectively associated with heavy use and alcohol and drug disorders [14, 27, 137].

Personality Traits

No single personality trait predicts alcoholism [239], but traits associated with the development of alcohol use disorders include novelty seeking [32] and sensation seeking [186, 289], traits that are often associated [58, 282]. The heritability of sensation seeking is unclear, with some twin studies suggesting that approximately half of the variance can be attributed to genetic factors [119, 121, 135], and another suggesting a much weaker influence of genetic factors [195]. Additional personality traits related to alcohol use disorders, albeit less consistently, are neuroticism/negative emotionality [288], impulsivity/disinhibition [191], and extraversion/sociability [125]. Similar traits have been examined in relation to drug use disorders. For example, research has shown that impulsivity/inhibition is reliably lower among individuals with drug abuse/dependence [38, 190], whereas negative emotionality tends to be higher [253, 282].

Subjective Reactions

Level of response to alcohol indicates the quantity needed to obtain an effect. Individuals with a low level of response need to drink more to obtain an effect. This is a genetically influenced characteristic associated with enhanced risk for alcohol use disorders [234]. Level of response varies by ethnicity. Several groups at high risk for alcohol use disorders show low response, including children of alcoholics, Native Americans, and Koreans [63, 198, 273], while high response is found among Jews [234], a group with relatively low levels of alcohol disorders [107, 174]. A low level of response predicts later onset of alcohol dependence in young adult males [232], and may contribute to transition from lighter to heavier drinking in individuals in a heavy-drinking environment [230]. Several chromosomal regions have shown suggestive linkage results to level of response [280] and an association with variations in the ADH1B gene (one of the genes that influences metabolism of alcohol in the liver) has been documented [57], but replication is needed.

Subjective reactions can also be characterized by whether they are positive or negative. A stimulating (reinforcing), rather than sedating, effect of alcohol has been identified in moderate/heavy drinkers [131], as well as untreated alcoholics [258]. In contrast, a flushing reaction to alcohol includes unpleasant physical sensations [124], found among Asians. A strong flushing reaction precludes drinking, while moderate flushing protects against alcohol dependence. Individuals also vary in their subjective responses to marijuana, and positive and/or negative responses are moderately heritable [180].

Psychiatric Comorbidity

Individuals with substance use disorders exhibit higher rates of mood, anxiety, and personality disorders as compared with the general population [35, 86, 87, 114, 154, 221]. For example, national surveys indicate that individuals with an alcohol disorder are approximately 3.0 times more likely to be diagnosed with major depression; the association between drug disorders and major depression is even stronger,

with odds ratios around 7.0 [36, 102]. A strong association has also been documented between substance disorders and antisocial personality disorder. The National Epidemiologic Survey on Alcohol and Related Conditions survey estimates that 39.3 and 72.4% of individuals with antisocial personality disorder meet criteria for lifetime drug disorders and alcohol disorders, respectively [79].

The strong and consistent relationships between substance disorders and other psychiatric disorders have prompted etiologic researchers to evaluate evidence for an underlying vulnerability to psychiatric disorder in general. Adult twin studies indicate at least moderate genetic heritability across disorder [146, 149, 182], and recent genetic studies have indicated specific genes associated with the transmission of several psychiatric disorder in general, rather than particular disorders [52, 274]. "Internalizing" and "externalizing" domains have been proposed as a means of organizing individual disorders into larger, more meaningful groups. Internalizing disorders are often characterized by the anxiety and depression domains, whereas externalizing disorders are often characterized by alcohol, drug, and antisocial personality disorders. Research into the validity and utility of broad versus narrow categorizations of disorder has been a major area of psychiatric research for decades [192], and remains ongoing [162, 163].

Genetics

Family and Twin Studies of Alcohol and Drug Dependence

Alcoholism [41, 205] and drug disorders [193] are familial. Genetic epidemiology studies of heritability use twin samples to compare concordance for a disorder between monozygotic (identical) vs. dizygotic (non-identical) twins. In these studies, significantly higher concordance in identical twins, who share 100% of their genes, compared with non-identical twins, who share only an average of 50% of their genes, indicates genetic heritability for a disorder. Twin studies of alcohol dependence show substantial heritabilities (50–60%) [118, 218]. Heritability estimates from studies of illicit drugs are more variable, perhaps due to more varied phenotypes (use, heavy use, abuse and dependence); for drug dependence, heritability estimates are similar to alcohol dependence [72, 147, 219]. For all substances, environmental factors appear to influence initiation and continuation of use, while genetic factors move individuals from use to dependence. Also, as noted above, environmental and social factors mediate the initiation and use of substances in childhood and adolescence, while genetic factors become more influential in the adult substance use and dependence [151]. Some twin studies investigating shared heritability of dependence on different substances showed high shared genetic variance between substances [149, 264] while other studies suggest that dependence on different classes of drugs is not genetically interchangeable [264]. Molecular genetics studies may be able to clarify these issues.

Genetics in Epidemiology Studies and Gene × Environment Interaction

The last 5 years have seen considerable progress in the genetics field in general, as well as in identifying genes whose variants show replicated results on relationships to the risk for alcohol and drug dependence. Some of the genes involved include those that affect the process of alcohol metabolism in the liver such as alcohol dehydrogenase 4 (*ADH4*), related to both alcohol [60, 94, 175, 177] and drug dependence [175, 177, 178]. Other well-replicated findings on genes related to the risk for substance dependence involve processes linked to neurotransmission. These include genes influencing gamma-aminobutyric acid, the major inhibitory neurotransmitter in the brain. Genetic variants in *GABRA-2* predict alcohol dependence in United States [42, 43, 59], Russian [170], and German [67, 247] samples, and the outcome of a behavioral treatment for

alcohol dependence in a multi-site study [12]. *GABRA-2* variants were also related to the risk for drug dependence [2]. The functioning of muscarinic cholinergic receptors underlies many brain functions, including attention, learning, memory, and cognition, all potentially related to addictive disorders. Genetic variants influencing this process include *CHRM2*, shown to affect the risk for alcohol and drug dependence [51, 176, 275] and related personality traits [60].

Although twin studies show that genetic and environmental factors are both important, few studies have addressed whether the relationship of specific genetic variants to alcohol and drug dependence is modified by environmental circumstances. This type of research question could be addressed by appropriately designed epidemiologic studies that collect DNA as well as interview information on risk factors. Until recently, a limitation on such studies was the need to extract DNA from blood samples, a difficult task in survey research due to many practical considerations. Fortunately, methods have recently become available to collect DNA through the use of saliva samples, making the inclusion of genetic variables much more feasible in epidemiologic research. An example of this approach includes a study showing that being exposed to childhood maltreatment interacted with a gene influencing stress reactions to predict early onset of drinking among adolescents [145]. Additional studies of this type are under way in Israel [248] and are being planned in the United States.

Studying the interaction between certain genes and specific environmental factors has important implications for the prevention and treatment of alcohol and drug use disorders. First, better knowledge in this area may help early identification of individuals who are unlikely to be able to use drugs or alcohol in moderation for early education, additional support or supervision. Second, the knowledge may help identify individuals exposed to particular stressors that would particularly benefit from intervention. Finally, clearer knowledge of the interaction of environmental with genetic effects may suggest new lines of investigation to determine the biological mechanisms of protective or risk-enhancing environmental events or conditions, which may eventually aid in developing better treatments.

Conclusion

In summary, a number of factors influencing the risk for substance dependence have been identified. Through trans-disciplinary research, epidemiologists and others can work together in the future to address multi-level factors conjointly.

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