CHAPTER THREE

Epidemiology of Drug Abuse: Building Blocks for Etiologic Research

Naimah Weinberg, Marsha Lopez and Wilson M. Compton
Division of Epidemiology, Services and Prevention Research, National Institute on Drug Abuse, Bethesda, MD, USA

1. INTRODUCTION

Addictions and related misuse of intoxicants are costly, distressing, and challenging problems on personal, clinical, and public health levels. Advances in the neuroscience of these conditions depend, in large part, on foundational understanding of the epidemiology of the phenomena. For instance, the recognition that addictions have a genetic basis derives from family, twin, and adoption epidemiology studies. The onset of addictions in adolescence with roots much earlier in childhood experiences also derives from observational studies of the conditions in broad populations. In the past 10 years, significant new epidemiologic approaches have been developed and applied to study the patterns, origins, and consequences of developmental behavior problems that point the way for fruitful basic science research.

This review covers both substance use (SU) and substance use disorders (SUD), drawing almost exclusively on studies using population-based rather than clinical samples. Such study samples (sometimes called "epidemiologic" or "community-based") offer greater generalizability and freedom from the biases and confounders that are inherent in the use of clinic-based samples (Armstrong and Costello, 2002). Most of the citations are drawn from longitudinal studies. Innovative approaches further enhance the utility of epidemiologic studies for understanding causality (Rutter, 2009).

An important caveat is that SU is not a precise term and is used differently by various researchers (Armstrong and Costello, 2002). When a cited study focuses particularly on substance initiation, that is, the age at which a substance is first used, this is indicated. For SUD, the cited studies generally employ standardized instruments to assess abuse and dependence based on criteria in the Diagnostic and Statistical Manual Version IIIR (American Psychiatric Association, 1987) or IV (American Psychiatric Association, 1994). Further, SU and SUD encompass a variety of licit and illicit substances. In this paper, most findings apply to multiple substances and when a finding relates only to a specific drug, this is indicated.

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References for this review were drawn from literature searches conducted using PubMed and other databases. However, this review presents new findings and innovative approaches in the epidemiology and etiology of SU/SUD, rather than a comprehensive review of all relevant research. As an increasingly strong body of research on SU and SUD is emerging using population-based, high-risk, and clinical approaches, only a fraction can be cited herein, and further reading can be found in the references.

2.1. EPIDEMIOLOGY

Tracking the shifting landscape of SU and SUD, a key goal of epidemiologic research, provides clues about etiology and informs prevention, treatment, and policy planning. On a frequent recurrent timeframe, three national surveys assess and report the prevalence of drug-using behavior and attitudes toward drugs in the general US population: the Monitoring the Future (MTF) study of U.S. 8th, 10th and 12th graders and linked longitudinal follow-up study (Johnston et al., 2013), The National Survey of Drug Use and Health (NSDUH) study of the U.S. populations ages 12 and older (Substance Abuse and Mental Health Services Administration, 2011), and the Youth Risk Behavior Survey (YRBS) of adolescent students (Centers for Disease Control and Prevention, 2010). While each survey tends to report slightly different estimates in any particular year, the overall trends in SU are consistent across the surveys over time. After peaking in the late 1970s, overall drug-use rates declined during the 1980s and then rose again during the first half of the 1990s. Since the mid/late 1990s, overall drug-use rates declined slowly or remained generally stable. Of course, within this overall pattern, many specific drug epidemics were observed. For example, rates of MDMA (ecstasy) use increased markedly in the late 1990s and then declined rapidly in the early 2000s.

In addition to the surveys that document trends in overall drug-use rates across the USA, periodic surveys of national samples also inform our understanding of drug using adult populations, especially the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) and the National Comorbidity Surveys (NCS). These are also highlighted as they emphasize the relationship of SU and SUD to other mental illnesses (Compton et al., 2007; Swendson et al., 2008).

Initiation: The age of initiation for specific illicit drugs varies by substance, although SU tends to start during adolescence. The NSDUH finds that among the nearly three million people ages 12 and older who reported using an illicit drug for the first time in the past year, 56.7% were under the age of 18 and the average age at initiation, among persons ages 12 to 49, was just under 19 years old (Substance Abuse and Mental Health Services Administration, 2011). According to the long-standing MTF study (Johnston et al., 2013), alcohol, tobacco, and inhalants demonstrate earlier patterns of initiation in comparison to illicit drugs such as cocaine powder and hallucinogens, which show a pattern of initiation in later adolescence. Additionally, among the MTF respondents, age of

initiation is generally earlier for the drugs perceived to be less risky. For most substances, age of onset has been reported as early as the 4th grade (about 10 years old), albeit at very low rates, with more rapidly increasing rates starting in the teenage years. Estimates of reported age of illicit drug initiation should be considered in the context of the limitations of this type of information. For example, the MTF study surveys 8th, 10th, and 12th graders who are enrolled and attending school; thus, dropouts and absentees who are more likely to have SU and early onset drug use are more likely to be captured in the 8th grade sample but not in the 12th grade sample (Johnston et al., 2013). Also, retrospective reports of age of onset are subject to recall biases. Despite limitations, however, these data provide useful information on trends in use over time.

Patterns of SU: After recent peaks in the mid- to late-1990s, a slow but steady decline in the overall reported SU among adolescents was seen until 2008. Since that time, overall rates of SU in adolescents have remained stubbornly steady. In 2012, nearly half of high school seniors reported having used an illicit drug at some point in their lives, and 40% had used in the past year (Johnston et al., 2013). Although marijuana is the most prevalent illicit drug reported, it is important to note that the while cigarette and alcohol use are legal among adults and thus not included in the "any illicit drug" category, their use is illegal among adolescents. Roughly, one out of every eight 8th graders, one third of 10th graders, and nearly half of high school seniors reported having been drunk in the year prior to survey. While the prevalence of cigarette use has dropped quite dramatically over the years, reductions in illicit drug use have been less substantial, such that estimates of reported illicit drug use now match or exceed those for cigarette use among adolescents (Figure 1, Johnston, et al., 2013). Estimates for specific illicit drug use reported by high school seniors in 2011 are presented in Table 1. Of note, the MTF study examined rates of so-called synthetic marijuana (sold under such trade names as "K-2" or "Spice") for the first time in 2011 and found that 11.4% of 12th graders reported using these substances during the past year. In 2012 past year use held at 11.3% of 12th graders. This important result provides evidence that newly created substances can quickly make their way into widespread consumption.

The patterns of drug use shift across different ages, with inhalants more commonly abused by children and early adolescents than by older adolescents and adults (Johnston et al., 2013). Most other substances are used more frequently by older adolescents and young adults with rates peaking in the twenties (Substance Abuse and Mental Health Services Administration, 2011). These patterns are meaningful as drug users who report inhalant use appear to have worse outcomes, including early initiation of other drugs and a higher prevalence of drug-use disorders, compared to users who did not report inhalant use (Storr et al., 2005; Wu et al., 2008). As seen in Table 1, after alcohol and tobacco, the most commonly used drugs reported by youth are marijuana, amphetamines, nonmedical use of prescription drugs, and hallucinogens; for those who go on to use other drugs such as cocaine, that use emerges more commonly in later years.

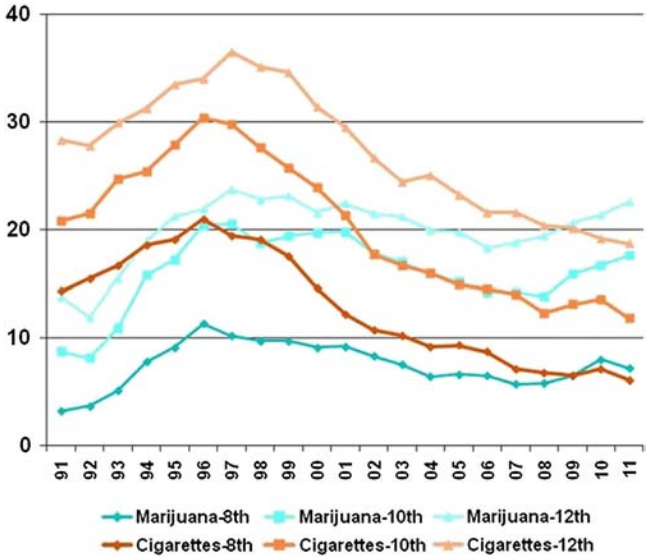

Figure 1 Past Month Cigarette and Illicit Drug Use among 8th, 10th, and 12th Graders in the US, Monitoring the Future Study (Johnston, et al., 2013).

Table 1 Prevalence of Past Year Drug Use[1] among 12th Graders, 2012 Monitoring the Future Study (Johnston, et al., 2013)

Drug	%
Alcohol	63.5
Marijuana/Hashish	36.4
Synthetic Marijuana	11.3
Amphetamines[1]	7.9
Vincodin[1]	7.5
Adderall[1]	7.6
Salvia	4.4
Tranquilizers[1]	5.3
Cough Medicine[1]	5.6
MDMA (Ecstasy)	3.8
Hallucinogens	4.8
OxyContin[1]	4.3
Sedatives[1]	4.5
Inhalants	2.9
Cocaine (any form)	2.7
LSD	2.4
Ritalin[1]	2.6
Ketamine	1.5
GHB	1.4
Methamphetamine	1.4

[1]Categories not mutually exclusive.

Polysubstance use: Research also suggests that polysubstance use—using multiple substances within a defined period of time—is a typical pattern of SU, especially among youth (Mitchell and Plunkett, 2000; Whitesell et al., 2006; Dierker et al., 2007; Connell et al., 2009; Connell et al., 2010). Among adolescents in secondary school, between 13% and 39% of adolescents may be described as polysubstance users (though the actual estimates vary by sample, reporting period, and definition of polysubstance use). For example, the 2005 YRBS found four types of users based upon past-month patterns of use among adolescents in grades 9–12: alcohol experimenters (38%), nonusers/abstainers (27%), occasional polysubstance users (23%), and frequent polysubstance users (13%) (Connell et al., 2009). Analyses of the 2001–02 National Study of Adolescent Health data identified five classes of students in grades 7–12 based upon use during the past month/year: low use (55%), alcohol only (15%), alcohol-marijuana (8%), cigarettes (8%), and three-substance use (14%) (Dierker et al., 2007). In addition, adolescent polysubstance use has been associated with significant deleterious outcomes, including substance dependence (Whitesell et al., 2006), smoking in adulthood (Dierker et al., 2007), and risky sexual behavior (Connell et al., 2009). A recent study using MTF data from senior high school students between 2002 and 2006 found that nearly 7 in 10 nonmedical users of prescription opioids reported co-ingestion of prescription opioids and other drugs (marijuana, alcohol, cocaine, tranquilizers, and amphetamines) in the past year (McCabe et al., 2012). Using data from a genetically informative longitudinal sample, Vrieze and colleagues (Vrieze et al., 2012) examined changes in correlations among symptoms of nicotine, alcohol, and marijuana abuse and dependence from ages 11–29; at younger ages use of these substances showed higher correlations, suggesting indiscriminate use, which declined with age as individuals showed a great preference for one substance over the others.

Differential patterns of SU: Patterns of drug use vary significantly by gender and ethnic group as well as by drug. For many specific drug types, males tend to report more use than females particularly as they get older (Johnston et al., 2013). Previous literature suggests that some of this gender difference may stem from males having greater opportunities to initiate drug use; once opportunity to use was controlled for, males and females had equal likelihood of using drugs (Van Etten et al., 1999). One notable exception is inhalants, which is reported by more females in the younger grades than by males (Swendson et al., 2008). White and Hispanic youth tend to report more overall drug use than African American youth; however, these differences vary by drug type and grade (Johnston et al., 2013). Additional details regarding racial and ethnic differences can be found in the respective reports of the major national surveys cited above.

Medication abuse: The profile of drug use has shifted over the past 10 years, with the recent emergence of medication abuse. As noted in Table 1, in 2012, many of the most prevalent drugs used by 12th graders are nonprescribed prescription or over-the-counter medications (Johnston et al., 2013) such as pain medications, stimulants, and sedatives.

Results from the 2009 YRBS indicate that one out of five U.S. high school students reported having taken a medication without a doctor's prescription, with rates of lifetime medication misuse rising from 15% among 9th graders to 26% among 12th graders (Centers for Disease Control and Prevention, 2010). These data also show that medication misuse is highest among white students, followed by Hispanic students, and lowest among African Americans, with no gender differences found; however, analyses of other data suggest that these trends may vary by drug (Sung et al., 2004). A review of both community-based and clinical studies of adolescents and college-aged subjects found higher risk for diverting and misusing stimulant medications by those who were white, had lower grade point averages, used immediate release rather than delayed-release formulas, and had symptoms of attention deficit hyperactivity disorder (ADHD), although stimulant misuse was found among those with and without ADHD (Wilens et al., 2008).

The problem of prescription opioid misuse has been particularly acute, with markedly increasing rates of nonfatal and fatal overdoses (Paulozzi et al., 2011). Of note, this report suggests an association between increasing rates of overall availability of prescription opioids with increasing rates of overdose mortality as well as geographic associations such that states with higher rates of prescriptions for opioids tended to have higher rates of overdose mortality. In addition, the increases in mortality related to prescription opioids have paralleled sharp increases in rates of treatment admission for opioid addiction over the past decade (Centers for Disease Control and Prevention, 2011).

A key concern is the source of prescription medications being diverted for nonmedical use. Data from all subjects in the combined 2009–10 NSDUH show that "friends or relatives" were the primary source for pain relievers (the most commonly abused prescription medication class), while physicians served as the direct source about 20% of the time (Figure 2). In turn, these friends and relatives reportedly obtained the medications from one doctor 80% of the time (Substance Abuse and Mental Health Services Administration, 2011). An analysis of adolescent subjects in the combined 2005-6 NSDUH data (Schepis and Krishnan-Sarin, 2008) found that those purchasing prescription medications illegally were more likely to be abusing other substances, while those who obtained prescription opioids from a physician were more likely to have had a major depressive episode in the past year.

Associated risks and consequences: Alcohol and drug use are associated with a variety of risky behaviors and related problems, even when a use does not progress to SUD. Drug and alcohol use serve as both distal and proximal risk factors for suicidal behavior and attempts (Esposito-Smythers and Spirito, 2004), possibly mediated by impulsive personality traits (Dougherty et al., 2004). Alcohol use in particular may have a causal effect on violence and vandalism (Felson et al., 2008), and is associated with other delinquent acts, such as shoplifting (Felson et al., 2008) and gambling (Duhig et al., 2007). Furthermore, SU is associated with increased risky sexual activity (Anderson and Mueller, 2008) and serious driving injuries or fatalities (National Highway Traffic Safety

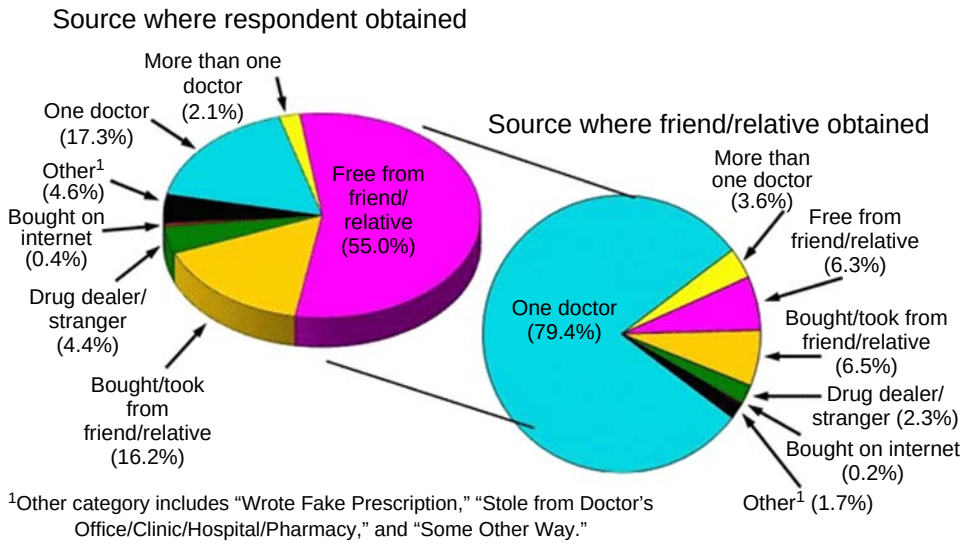

Figure 2 People abusing analgesics mostly do not obtain them by prescription: Most recent source of abused analgesic for household residents in the USA ages 12 and older who report abusing analgesics *(SAMHSA, 2010–2011 National Survey on Drug Use and Health)*.

Administration, 2010). One longitudinal study found increased risks for adult substance dependence, herpes infection, early pregnancy, and crime associated with early SU, even in the absence of conduct disorder (Ogders et al., 2008).

2.1.1. Substance Use Disorders

Adolescence is not only a period of experimental drug usage, but it is also a period during which young people have high potential to develop drug-use disorders and other longer term negative outcomes. Studies of adult samples using DSM-IV criteria for SUDs have found similar patterns of onset across all substances during adolescence and early adulthood, peaking at about 20 years of age, with onsets after 25 quite rare (Compton et al., 2007). Thus, adolescence is a prime period of risk for the development of SUDs.

Recent findings from the NSDUH documented consistent rates of DSM-IV drug-use disorders (i.e. DSM-IV abuse or dependence on illicit drugs) over the past decade, varying little from 2002 (3.1%) to 2010 (2.8%) among those ages 12 or older (Substance Abuse and Mental Health Services Administration, 2011). While the prevalence of abuse or dependence on illicit drugs in 2010 was higher among all males (3.6%) than females (2.0%) in the survey, the rate was higher for females (4.9%) than males (4.6%) among subjects between the ages of 12–17. Rates of SUD were also found to vary by ethnicity: Asian Americans had lower rates of abuse or dependence on illicit drugs (1.3%) than African Americans (4.0%), Hispanic or Latino (3.5%), Whites (2.5%), and American Indian or Alaska Native (6.3%) populations ages 12 and older.

2.1.2. Psychiatric Comorbidity

Psychiatric disorders commonly co-occur with SU and SUD and are discussed further below in the section on etiology. The risk of developing SU/SUD in the presence of comorbid psychiatric disorder varies by study, but has consistently been found to be about three times greater in comparison to those without a psychiatric disorder (Armstrong and Costello, 2002). Among adults, strong associations of SU/SUD and psychiatric illnesses are the rule rather than the exception (Swendson et al., 2008). Associations are strong and specific, especially for antisocial personality disorder (and other personality disorders) and bipolar disorder (BPD).

As noted above, SU is frequently comorbid with psychiatric illnesses and may increase the risk for psychiatric disorders in vulnerable individuals. For both depression and anxiety disorders, there is evidence for bidirectional relationships with alcohol disorders, where internalizing disorders may precede or follow adolescent alcohol use (Nurnberger et al., 2002; Marmorstein, 2009; Kushner et al., 2000). While substances, particularly alcohol, may have depressive effects or may elicit anxiety symptoms on withdrawal, this comorbidity may also be the result of common liability factors leading to both SU and internalizing disorders (Nurnberger et al., 2002; Kuo et al., 2006). Cigarette smoking in adolescence may have a similar bidirectional relationship with depression, *contributing* to the onset of depression in some individuals (Windle and Windle, 2001) although possibly *resulting* from depression in others, as discussed further below. Cannabis use has been linked in numerous studies to an increased risk for psychotic disorders, and use in adolescence may pose a particularly elevated risk (Henquet et al., 2008), although accounting for only a small fraction of the onset of psychosis; a variety of mechanisms have been suggested, including gene–environment interaction (GxE) (Henquet et al., 2008). In fact, a recent population-based Dutch study has found a bidirectional relationship between vulnerability to psychosis and cannabis use in adolescents (Griffith-Lendering et al., 2013). The gravity and costs of psychiatric outcomes underscore the clinical and public health importance of understanding and preventing SU and SUD.

2.2. ETIOLOGY

SU and SUD result from a complex interplay of individual-level, environmental, and developmental factors. In discussing etiology, the term "risk factor" indicates a variable that has been found to be associated with an increased risk of an adverse condition; however, even if a risk factor precedes an outcome temporally, it cannot be assumed to be causal. For this discussion, the term "causal" is used if there is evidence that the risk factor contributes directly to the development of SU or SUD, and "risk indicator" is used for factors that may serve as proxies for a causal risk factor but which have no demonstrated role themselves in the causal chain.

2.2.1. Gene–Environment Interplay

While a full discussion of the role of genetics and epigenetics in SU and SUD is beyond the scope of this review, a few key concepts of gene–environment interplay are essential for the ensuing discussion of etiology; further reading can be found in the references.

Gene–environment correlation (rGE) is a complex concept that needs to be considered in studies of psychopathology, in order to help discriminate true causal risk factors from indicators of risk. In rGE, genetic factors contribute to the likelihood that an individual will be exposed to particular types of environments. Three types of rGE have been described (Dick et al., 2009a; Rutter et al., 2006). In passive rGE, parental genes set the stage for the type of environments to which children are exposed; for example, parents with alcohol dependence are more likely to provide a chaotic home life. In active rGE, a child may seek out certain environments based on genetic propensities (Kendler et al., 2007). In evocative rGE, a child's characteristics (such as genetically based temperament features) may evoke certain responses from others, such as harsh treatment of children with difficult temperaments. Thus, factors that appear to be environmental in origin may actually arise from genetic predispositions in the parents or children.

In GxE, the effects of environmental exposures vary by an individual's genotype, or conversely, genetic effects are moderated by environment (Dick et al., 2009a); this occurs in normal and pathological development. In a large study of adoptees in Sweden, both genetic and environmental factors were implicated in the onset of SU/SUD, with important synergies documented such that those with the highest genetic risk showed a stronger association of environmental risk factors with SU/SUD outcomes compared to those with lower genetic risk (Kendler et al., 2012). Environmental effects can also enhance resilience in vulnerable youth. Recent findings on the effects of parental monitoring interacting with genotype (Brody et al., 2009a) exemplify GxE and are discussed below in the section on environmental risk factors.

Heritability refers to the proportion of variance of a trait in a population that can be attributed to genetic influences. For SUD, heritability estimates in adults range from 45% to 79% (Dick and Agrawal, 2008). However, it is important to remember that heritability is a population statistic, and does not indicate the degree of genetic contribution in any individual case (Rutter et al., 2006); in fact, as a complex disorder, SUD most likely involves a large number of genes (Dick and Agrawal, 2008) many of which are likely to be of small effect (Rutter et al., 2006). Furthermore, heritability estimates will vary with the degree of exposure to relevant environmental conditions in a study population (Rutter et al., 2006); thus, heritability and environment are confounded and there is never a fixed level of heritability for a particular disorder.

Numerous studies have found that heritability of SUD rises with age and with progression of SUD (Dick et al., 2009a; Hopfer et al., 2003), suggesting that genetic factors play an increasing role in the etiology of SUD as individuals pass through later adolescence into adulthood and as their SU advances to heavier use and addiction. Heritability

studies have also shown that much of the genetic risk for SUD is nonspecific in regard to choice of substance (Hopfer et al., 2003; Iacono et al., 2008), although there are also genetic vulnerabilities to dependence on licit vs illicit substances or specific substances (Dick and Agrawal, 2008; Iacono et al., 2008), perhaps most strongly for nicotine (Hopfer et al., 2003). In addition to genetic vulnerability to SUD, there is evidence for genetic predisposition to a constellation of externalizing behaviors across development, including conduct disorder (CD), ADHD, and SUD (Dick and Agrawal, 2008; Iacono et al., 2008); Figure 3 presents a simplified model of these findings.

Twin studies provide much of the data concerning the genetic liability for SU and SUD because they can explicate the causal nature of environmental factors separate from inherited in the etiology of psychopathologic disorders (Rutter, 2009; Hopfer et al., 2003). For instance, comparisons of monozygotic and dizygotic twins can yield estimates of the relative contributions of genetic, shared, and nonshared environmental factors at various developmental stages. Comparisons of exposed and unexposed twins (co-twin control method) can offer insights into the causal role of environmental factors, as can studies of the offspring of monozygotic twins, who are genetic half-siblings raised in different environments.

While a discussion of epigenetic mechanisms in addiction is beyond the scope of this review, it represents another example of gene–environment interplay with a potentially key role in drug-abuse trajectories, including in the effects of early initiation of drugs as discussed below (Volkow, 2011; for a review, see Satterlee, 2013).

2.2.2. Psychiatric Risk Factors

As noted above, psychiatric disorders are frequently comorbid with SUD, less so with SU. Examining each major cluster of psychiatric disorders illuminates the varying nature of the relationship between these disparate conditions.

Conduct disorder (CD): Early CD has consistently been found to constitute a risk factor for later SU and SUD in both males and females (e.g. Sung et al., 2004; Fergusson et al., 2007; Disney et al., 1999), regardless of the presence of other comorbid disorders. However, it is not clear whether CD is a causal risk factor for SUD or an indicator of risk. On one hand, some of the relationship appears to have a strong genetic base, where both CD and SUD constitute manifestations of an inherited predisposition toward behavioral disinhibition (Iacono et al., 2008). On the causal side, CD may predispose to SU through association with deviant peers; however, social factors would not account for the progression to SUD, and must be evaluated in light of studies showing heritable influences on a peer choice (Kendler et al., 2007). Several prevention studies are underway that may ultimately help clarify both the role of CD and opportunities for intervention; for example, a manualized behavior therapy program for disruptive behaviors in middle childhood demonstrated reduced SU in adolescence (Zonnevylle-Bender et al., 2007), although it remains to be seen whether later SUDs were affected. Another

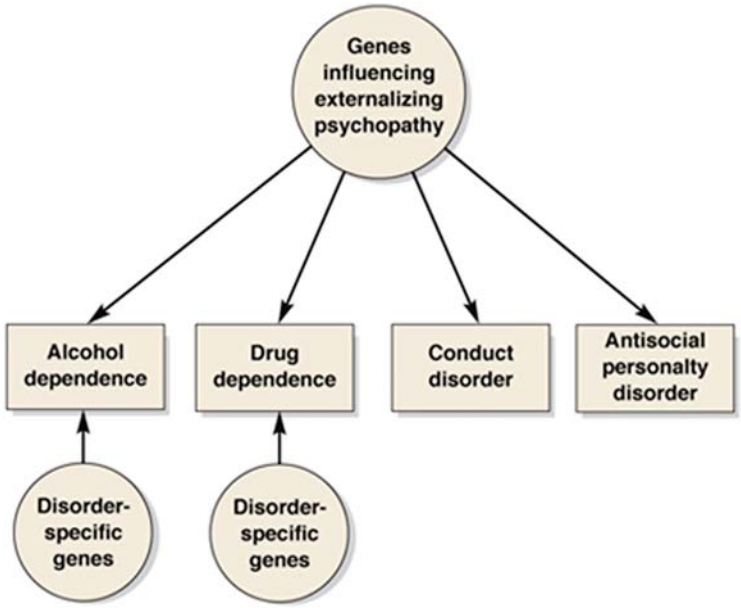

Figure 3 Common Genetic Factors for the Externalizing Disorders.

study found that an intervention to improve parenting skills had a particularly strong impact on reducing high-risk behaviors in adolescents at greatest genetic risk (Brody et al., 2009b), thus supporting the role of gene–environment interplay in both risk and resilience in high-risk populations (Iacono et al., 2008). Despite the strong risk for SUD that CD poses, it should be noted that the majority of those with SUD do not have a history of CD (Sung et al., 2004).

Oppositional defiant disorder (ODD): Most prior research on ODD and SUD has treated ODD as a comorbid condition with other externalizing disorders (e.g. King et al., 2004; August et al., 2006), and it is not clear what role if any ODD plays in the risk for SUD. One longitudinal study found that ODD was associated with neither SUD risk nor with progression from SU to SUD (Sung et al., 2004). A retrospective study found that childhood and adolescent ODD predicted SUD in adulthood, even in the absence of a history of CD and even when the ODD remitted (Nock et al., 2007). Given these and other findings on the psychiatric risks associated with ODD (Copeland et al., 2009), it seems that further prospective study is warranted, particularly to clarify whether ODD is an indicator of risk and whether interventions could possibly reduce the chances of adverse outcomes.

Attention deficit hyperactivity disorder (ADHD): Given the high prevalence of childhood ADHD and of the use of stimulant medications in the U.S., the possible role of childhood ADHD and of ADHD treatments in the etiology and course of SUD are of

particular public health importance and clinical significance. In contrast to many clinical studies, numerous population-based prospective studies have *not* found ADHD to constitute a risk factor for SUD, once comorbid CD and ODD are taken into account (Fergusson et al., 2007; Disney et al., 1999; August et al., 2006; Pardini et al., 2007; Bussing et al., 2010). While this may offer some reassurance regarding children with uncomplicated ADHD, significant subgroups of children with ADHD may be at greater risk, and these may be the populations that more often present clinically. Clearly, those with comorbid CD face an increased risk (e.g. Fergusson et al., 2007), and the ADHD–ODD combination may pose an elevated risk as well (August et al., 2006). Findings are contradictory as to whether ADHD augments the risk from CD (Fergusson et al., 2007; Flory et al., 2003) or whether the presence of multiple externalizing disorders may indicate problems with behavioral disinhibition, often of a familial nature, which may be manifested by these childhood disorders and SUD (Iacono et al., 2003; Tarter et al., 2003). Additionally, certain features of ADHD may relate to specific outcomes: hyperactivity/impulsivity appears to pose particular risk for SUD (Elkins et al., 2007; Tarter et al., 2007), while inattention may pose a greater risk specifically for tobacco use (Burke et al., 2007) or nicotine dependence (Elkins et al., 2007); these findings underscore the potential utility of studying dimensional approaches to risk. Those whose ADHD persists beyond adolescence may also face higher risk (Kessler et al., 2006). Several longitudinal studies of clinical populations have examined SUD outcomes of childhood ADHD and associated features; for a detailed review, see (Looby, 2008).

Contradiction and controversy surround the question of the potential role of prescription stimulant medication in the onset and course of SU and SUD. Numerous methodological challenges make it very difficult to distinguish either a causal or protective role from correlations. These include referral biases; differential attrition (wherein those most likely to use substances are more likely to be lost to follow up); systematic differences between subjects and controls (such as age or socioeconomic status); changes in drug-abuse trends over time; differences between study samples on relevant factors such as comorbidity; and the nonrandomized nature of most treatment studies (self-selection factors) (Armstrong and Costello, 2002).

Concerns about stimulant medications arose from the sensitization hypothesis, wherein exposure to stimulant medication may induce neurochemical changes that lead to drug craving, based on alterations in the dopamine system (Looby, 2008; Volkow and Swanson, 2008). One community-based longitudinal study (Winters et al., 2011), a recent meta-analysis (Humphreys et al., 2013), and a number of clinical follow-up studies (see reviews by Looby, 2008; Volkow and Swanson, 2008) have not found elevated rates of SUD in those who were prescribed stimulant medications in childhood, which should provide reassurance that stimulant medications do not appear to increase the risk for a later SUD. Alternatively, some authors have found reduced rates of SUD among those receiving stimulant medication, and have posited a protective effect of stimulant

medications in ADHD based on reductions in impulsivity and in social and school failure, as well as stimulant effects on reward circuits in the brain (reviewed in Faraone and Wilens, 2007). Unfortunately, a number of doubts have been raised about these findings derived from nonrandomized studies that are subject to the methodological challenges mentioned above, particularly systematic differences between subjects and controls (Volkow and Swanson, 2008). Moreover, by adulthood, prior treatment with stimulants was no longer associated with decreased risk for alcohol, drug, or nicotine use disorders (Faraone and Wilens, 2007; Biederman et al., 2008), suggesting that, at best, the treatment delayed an SUD. Age at initiation of stimulant treatment has been hypothesized to affect later risk for SUD (Mannuzza et al., 2008), but findings thus far are contradictory (Biederman et al., 2008; Mannuzza et al., 2008). Based on this review, prevention of SUD cannot currently be supported as a justification for the prescription of stimulant medication (Swanson and Volkow, 2009).

Further data, ideally from randomized study designs, and creative approaches to interpreting available data, such as trajectory analyses, are needed to disentangle this question; for example, subjects in the Multimodal Treatment of ADHD (MTA) study (Molina et al., 2007) will be followed through early adulthood with SUD assessments, and a wealth of covariates, including randomized ADHD treatments at ages 7–9, will be studied, although this study, too, is subject to methodological concerns (Hazell, 2009). Thus far, the MTA cohort, followed up naturalistically for eight years (mean age at follow up of 17), shows neither a protective effect nor an increase in SU or SUDs in adolescence related to medication history (Molina et al., 2013).

Bipolar disorder: Both epidemiologic (Glantz et al., 2009) and clinical (Strakowski et al., 2000) studies have found high rates of comorbidity between SUD and BPD in adults, but population-based data on BPD as a precursor to SUD are few, probably due to low rates of BPD in the general population (Lewinsohn et al., 2004). Evidence from clinical samples supports SUD as either an antecedent (Strakowski et al., 2000) or consequence (Wilens et al., 2004) of BPD, and the association may in some cases be familial (for a review of possible mechanisms, see Strakowski et al., 2000). A bidirectional pattern was found in a population-based study using NESARC data, wherein nicotine dependence and BPD each predicted the onset of the other, and the trajectories differed significantly based on which disorder developed first (Martínez-Ortega et al., 2013). These data suggest that individuals with adolescent BPD merit monitoring and education regarding risk for SUD.

Depression: Findings on depression as a risk factor for SU and SUD have been quite contradictory. For example, one population-based study (Costello et al., 1999) reported that depression was associated with higher rates and earlier onset of SU and SUD, while another (Rohde et al., 2001) found that adolescent alcohol use disorder predicted depression in early adulthood rather than the reverse. Analyses of the National Study of Adolescent Health data showed a bidirectional relationship (Marmorstein, 2009),

where depressive symptoms and alcohol problems predicted each other. Similar findings were reported using data from NESARC, where alcohol use disorders and cannabis use disorders, individually or comorbidly, showed a bidirectional relationship with major depressive disorder (Pacek et al., 2013). Numerous factors may account for these inconsistencies: using categorical vs dimensional approaches to define the outcomes, age at assessment, gender differences, and comorbidity (for a detailed discussion see Marmorstein et al., 2010a); moreover, much of the literature studies only alcohol or nicotine, and it is not clear whether these relationships differ by substance. In some cases, this bidirectional relationship may result from genetic factors that predispose individuals to both depression and SU (Nurnberger et al., 2002; Kuo et al., 2006), but this merits further exploration. One factor that has not been addressed in these studies is caffeine use in early adolescence, and its possible associations with sleep and mood disturbances (Whalen et al., 2008). The clinical implications of all these relationships are significant and more research in this area is clearly needed.

Anxiety disorders: As with depression, findings regarding anxiety disorders and SUD have been inconsistent. Several studies have found that anxiety disorders are not associated with later SUD (e.g. Pardini et al., 2007; Goodwin et al., 2004) after controlling for potential confounders, while another recent study found that generalized anxiety predicted early use and greater progression to problematic marijuana use in boys (Marmorstein et al., 2010b). One review found evidence for bidirectional relationships between anxiety and alcohol disorders, wherein the presence of either increased the risk for the other (Kushner et al., 2000). Analysis of data from the NCS replication study found that social phobia, panic disorder, and agoraphobia tended to occur prior to SUDs, while generalized anxiety disorder tended to occur after onset of at least one SUD (Marmorstein, 2012). Thus, it may be that particular types of anxiety disorders pose risk for, or provide protection from, SU and SUD, and that the risk varies by substance and by developmental stage. Further studies are needed that consider these factors.

Personality disorders: One longitudinal population-based study found that borderline, histrionic, and narcissistic personality disorders in early adolescence predicted later SUD, after controlling for relevant risk factors (Cohen et al., 2007). Studies drawing on follow-up data in the NESARC found consistent associations in adults of several personality disorders with progression to problematic SU (Compton et al., 2013) and specifically of antisocial, borderline, and schizotypal personality disorders with persistent SUD (Hasin et al., 2011).

Learning disabilities: A population-based study found that learning disabilities (LD) were associated with later SUD as well as other psychiatric disorders at age 19 (Beitchman et al., 2001); however, the risk may be nonspecific (Beitchman et al., 2001) and potentially confounded by biological and psychosocial risk factors (Weinberg, 2001). Thus, while children with LD may be at increased risk for SUD, the LD may be an indicator of general risk rather than a specific causal factor.

Multiple comorbid disorders: Few studies have examined the impact of comorbid internalizing and externalizing disorders on SUD risk, but there are suggestions that this constellation represents a particularly high risk; for a review of this potentially important area, see (Pardini et al., 2007; Tully and Iacono, in press).

Self-medication: The use of alcohol and drugs, particularly by those with depression or anxiety, is often characterized as "self-medication", but little scientific evidence exists to support this theory. While some individuals with anxiety disorder may find temporary relief in SU (Bolton et al., 2006), it is important to approach such explanations with caution: most individuals with internalizing disorders do not develop SUD; many substances, particularly alcohol, are CNS depressants that can exacerbate depression or cause anxiety symptoms on withdrawal; and retrospective reports of "self-medication" may actually represent efforts to rationalize addiction (Vaillant, 1983). Work on integrating the neurobiology of addiction with affective and motivational states is potentially illuminating and needed.

Alternative approaches to understanding risk: New and exciting approaches have been developed to help delineate the developmental psychopathologic roots of SU and SUD. In contrast to categorical approaches, where a subject is classified as having or not having a disorder, dimensional approaches may analyze individual symptoms or other quantifiable variables to capture the dimensions of risk (e.g. Iacono et al., 2008; Elkins et al., 2007). Trajectory analyses test causal hypotheses by classifying individuals by their risk for a particular outcome and analyzing whether an environmental circumstance alters the trajectory (Rutter, 2009), and this type of analysis has been applied to drug-abuse research. Propensity score matching aims to correct for selection biases through scores that reflect the probability of being exposed to a hypothesized causal agent (Rutter, 2009). Endophenotypes are hereditary characteristics associated with risk for a condition that are not symptoms of the condition themselves; one example is reductions in the amplitude of P300 brain waves associated with behavioral disinhibition (Iacono et al., 2008). Integrating imaging and other neurobiological approaches with epidemiologic research may also yield important insights (Compton et al., 2005). It is hoped that these approaches will be applied more widely to enhance understanding of the mechanisms of risk and opportunities for intervention.

2.2.3. Early Use

The role of early SU in later onset of SUD is very important but not yet clear. It is well-established that early initiation of SU is significantly associated with future SUD (Chen et al., 2009), even after controlling for comorbid psychiatric disorders (Sung et al., 2004). Less clear is whether early use plays a causal role in later SUD, such that delay in use might protect against SUD, or whether early use is a risk indicator. A number of studies suggest that early use is a nonspecific risk indicator associated with multiple forms of adult psychopathology (McGue and Iacono, 2005) and that common genetic factors

account for both early initiation and later SUD (e.g. Sartor et al., 2009). Early cannabis use in particular has been associated with progression to other illicit drug use (Lessem et al., 2006; Lynskey et al., 2003), however, a recent retrospective twin study suggests that cannabis use itself, regardless of age of initiation, is associated with increased risk for SUD (Grant et al., 2010). A natural experiment design compared prevalence of alcohol and SUDs in adults who were exposed to different minimum legal drinking age laws in the 1970s and 1980s (Norberg et al., 2009); those for whom it had been legal to purchase alcohol before age 21 were more likely to report symptoms of an alcohol or drug-use disorder in adulthood, even decades later, and the association seemed less related to age of initiation of drinking than to patterns of drinking in late adolescence. Another recent study using retrospective twin data found evidence for a GxE between first use of alcohol and later alcohol dependence (Agrawal et al., 2009); this finding merits replication with other samples and drugs as a fruitful way to understand this risk and the potential impact of preventive interventions. An interaction between early smoking and genetic vulnerability was also found in a large meta-analysis (Hartz et al., 2012), where early onset smokers with a known risk allele for smoking were significantly more likely to become heavy smokers in adulthood than carriers of the risk allele who were late-onset smokers. It is possible that other neurobiological and epigenetic changes take place with early use, and further work in this important area is needed. Although it is not clear whether delaying early use will prevent later SUD, there are ample other reasons to delay or prevent the use of substances by adolescents, and to treat early use as a risk indicator.

A particular pattern of early use has generated the "gateway hypothesis" of drug abuse in which the first exposures to alcohol, tobacco, and marijuana are causally linked later use of other drugs (e.g. cocaine, amphetamines or opioids, Kandel, 2003). Overall, the trajectory in which cocaine, amphetamine, and other drugs are nearly universally preceded by use of alcohol, tobacco and marijuana is well-established but the reasons for this trajectory are less certain. Common vulnerability to the multiple substances has been suggested (Morral et al., 2002). In contrast, a more recent animal study (in mice) generally supports a causal gateway pathway in which prior exposure to nicotine induces epigenetic changes that enhance responses to cocaine (Levine et al., 2011). This work included a demonstration that these basic research findings are consistent with human population data, and if substantiated, the suggestion is that reducing nicotine exposure by youth may reduce cocaine (and possibly other) drug addictions (Volkow, 2011).

2.2.4. Environmental Factors

A large and long-established literature has documented numerous environmental factors that correlate with SU and SUD (Galea et al., 2004). Applying newer strategies to distinguish causal risk factors and moderators of risk from simple correlations illuminates the mechanisms by which the interplay of environmental factors with individual-level

factors can increase or ameliorate risk over the course of development. These methods include studies of gene–environment interplay, natural experiments, and prevention studies that can inform etiology.

In discussing the impact of environmental factors, it is important to distinguish those that may impact SU (initiation or low-level use) from factors that influence the progression to SUD. While environmental factors contribute significantly to onset of SU, genetic factors play an increasingly strong role in vulnerable individuals who initiate SU, as use progresses to abuse and dependence and as individuals progress through adolescence to early adulthood (Dick et al., 2009a; Hopfer et al., 2003). However, those who are genetically vulnerable may also be both the most vulnerable to environmental adversity (Hicks et al., 2009; Kendler et al., 2012) and the most likely to derive benefit from protective features in the environment (Brody et al., 2009b; Dick et al., 2009b).

Family circumstances: While family socioeconomic status alone does not clearly relate to drug initiation (Galea et al., 2004), family adversity is associated with a greater prevalence of drug use and drug-use disorders later in life (Galea et al., 2004). Two recent studies have started to shed light on the potential role of family circumstances in behavioral problems that can lead to an SU. A natural experiment found that adults whose families were moved out of poverty due to tribal casino profits (thus, unrelated to family characteristics) during adolescence experienced reduced levels of CD and ODD in adolescence, and lower rates of alcohol and cannabis abuse and dependence in adulthood, providing support for a social causation role in these high-risk disorders (Costello et al., 2010). A twin study found a GxE between stressful life events (such as parental divorce or family financial or legal problems) and offspring externalizing disorders (Hicks et al., 2009), offering further support for a causal role for family adversity in high-risk behaviors; further follow up to assess for effects on SUD is anticipated.

Early stress and child abuse: Although a discussion of the psychobiological effects of early stress on development and risk for SU/SUD is beyond the scope of this review (Sinha, 2008), a few epidemiological findings will be highlighted. Individuals presenting for treatment often report a history of early trauma; however, clarifying the role played by abuse and neglect in the etiology of SU/SUD is very challenging, given that these early stressors tend to occur in families that confer genetic risk for SU/SUD, along with other adverse environmental conditions, including prenatal substance exposure (De Bellis, 2005). Some groups have applied innovative twin designs to control for the psychosocial effects of child abuse (Sartor et al., 2008). One study using an offspring of twins approach reported that child sexual abuse, but not child physical abuse, is associated with an increased risk for cannabis abuse and dependence in adolescence and young adulthood, beyond that posed by genetic and other environmental risk factors (Duncan et al., 2008); this is consistent with findings for other substances. Further integration of the roles of genetic, environmental, and developmental factors in response to stress is anticipated.

Parenting: Parenting qualities, and in particular parental monitoring, have long been associated with SU (Eaton et al., 2009). A recent meta-analysis describes the methodologic challenges in studying this important area and confirms a strong link between parental monitoring and reduced marijuana use in adolescents (Lac and Crano, 2009). However, it has been difficult to assess whether poor parental monitoring is a causal risk factor or a demonstration of rGE. On one hand, a recent study found that "parental monitoring" was more a function of the child's personality relating to a tendency to disclose information to parents, rather than an active behavior by the parents (Eaton et al., 2009), supporting a reconceptualization of parental monitoring. On the other hand, another recent study has shown that high levels of involved-supportive parenting were associated with reduced SU in youth who carried a genetic allele associated with increased risk (Brody et al., 2009a); a test of the data ruled out rGE as an explanation. A similar moderating effect of parental monitoring on behavioral outcomes in those with a different high-risk genotype was found in another community sample (Dick et al., 2009b). Moreover, an intervention to improve parenting reduced risk behaviors in adolescents at increased genetic risk (Brody et al., 2009b), providing further support for a protective role for positive parenting, particularly for those at highest risk. The role of parental monitoring as either a marker of risk or an opportunity for intervention is an important and potentially fruitful subject for future research.

Sibling influences: Although previously little studied, recent findings using genetically informative approaches have reported significant environmental influence by siblings on the development of externalizing disorders including drug use (Hicks et al., 2013), and that siblings closer in age are more likely to resemble one another in drug-use risk compared with those further apart in age, with older siblings more likely to transmit risk to those younger than the reverse (Kendler et al., 2012)

Religiosity: Various measures of religiosity among teens are strongly associated with reduced nicotine and alcohol use (Kendler and Myers, 2009; Timberlake et al., 2006), but the mechanisms remain unclear. Genetically informed approaches suggest that there are both genetic and environmental components to religious practice (Kendler and Myers, 2009), and that religiosity may moderate these factors (Timberlake et al., 2006), but more study is warranted.

Prenatal exposure: A full discussion of the risks associated with prenatal exposure to alcohol, nicotine, and illicit drugs is beyond the scope of this review. Clearly these environmental factors are experienced in high-risk families, and sorting through the relative roles of genes, exposure, and their interplay is complex and challenging (Glantz and Chambers, 2006). A number of studies are underway to follow prenatally exposed samples into adolescence and to apply sophisticated methodology to understand the contributions of these exposures to adverse outcomes (see National Institute on Drug Abuse, 2010).

Peers: Peer deviance has long been regarded as an environmental risk factor for SU (Gillespie et al., 2009), but recent work has started to question this role in the causal chain.

Based on retrospective data and twin modeling, peer group deviance appears to result from genetic as well as environmental factors, and in fact may be more a result of cannabis use than a cause (Gillespie et al., 2009). Furthermore, similar analyses have found that genetics play an increasing role in the choice of peer groups as adolescent's age and move away from parental influence (Kendler et al., 2007). Thus, what appears to be peer influence may be in part the result of active rGE, wherein an individual seeks out deviant peers based on genetic predisposition as well as environmental influences. More work in this key area is anticipated.

Schools: While schools are often the site of preventive interventions for SU/SUD, there is little research on the role of school factors in the etiologic chain. One cross-sectional study found that aggregated school attitudes disapproving of drug use (school norms) were related to reduced probably of SU, more strongly for 8th and 10th graders than 12th grade students (Kumar et al., 2002), even among those who personally did not disapprove of SU. In one intriguing study, student norms regarding smoking were found to moderate the heritability of daily smoking in high school, although genetic factors remained strong contributors (Boardman et al., 2008). Further investigations of school interventions are underway and needed to clarify the potential role of school norms.

Neighborhood factors and drug availability: While neighborhood disadvantage has been reported to be related to SU (Fite et al., 2009), it is not clear whether neighborhood factors play a direct causal role or serve as risk indicators. A recent study emphasizing the interrelationships among influences on adolescent behavior found that neighborhood influences are mediated through parenting and peer factors (Chuang et al., 2005). Moreover, drug availability, long considered the quintessential environmental factor, may (like peer influences) be due in part to active rGE, where high-risk youth seek out environments where they are more likely to be exposed to drugs (Gillespie et al., 2007).

2.2.5. Development

SU and SUDs are clearly developmental phenomena, with onset typically in adolescence, and changing expression associated with developmental trajectories, as individual-level factors interact with environmental. This review has incorporated a developmental perspective, but does not include a full discussion of the roles of pubertal changes, adolescent brain development, and shifts in roles and relationships as they impact SU and SUD (Windle et al., 2008; Brown et al., 2008).

3. CONCLUSIONS

Epidemiologic research has contributed vital findings on patterns, comorbidity, and etiology of SU/SUD, which can help guide future neuroscientific investigations. Ongoing surveillance and analyses of existing data will continue to provide such needed information. Increasingly, sophisticated methods for parsing out the causal roles of identified risk factors, and incorporation of genetic, neuroimaging, and psychophysiological

approaches into prospective and developmentally sensitive epidemiological studies, will further enhance the value and relevance of these studies. This review highlights four key sets of findings with implications for neuroscience:

1. Comorbidity: Psychiatric disorders commonly co-occur with drug-use disorders; this is the rule, rather than the exception. In some cases, both types of disorders may be manifestations of a common underlying genetic diathesis, particularly for the externalizing spectrum as discussed above. In others, SU may precipitate the onset of psychiatric disorder to which the individual was already vulnerable. For many disorders, there may be a bidirectional relationship, where the presence of either a psychiatric disorder or a drug-use disorder increases the risk for the other. These relationships are very important to investigate to understand risk and treatment, and comorbidity should be incorporated into studies of both animal models and human subjects.
2. Polysubstance use: While much of the substance abuse research literature focuses on single drugs of abuse, the reality as evidenced from epidemiologic studies is that individuals tend to use multiple drugs, either in sequence as shown in the gateway and progression studies, or within the same time period (i.e. within the same day, week or month). Both animal models and human studies need to incorporate polysubstance use into their approaches to forward true understanding of the phenomenon of SUD, and methodologies need to be developed to overcome the significant conceptual and feasibility challenges to doing so.
3. The role of environment: As discussed above, environmental factors play key roles in the exposure to and initiation and progress of SU as well as vulnerability to SUDs, through such mechanisms as stress responses, GxE, and epigenetics. The findings that those at genetic risk may be most vulnerable to environmental adversity highlight the significance of this interplay. Including environmental factors in etiologic and animal models will help refine understanding of vulnerability to SUDs.
4. The role of development: The findings cited above on the impact of timing of drug initiation (early use), gateway drugs and progression, and epigenetics, all highlight the importance of taking developmental stage and developmental sensitivities into account in human laboratory studies and animal models of drug abuse.

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