



Risk factors for addiction

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KEYWORDS:

Substance abuse;
Risk factors;
Adolescence;
Addiction;
Dependence

Major risk factors for addiction include those of the environment, more likely to affect initiation of use, and of the individual, where genetic factors are more likely to affect progression from use to dependence. An understanding of these risk factors will help the physician to counsel those at risk to avoid the initial use of or slow or stop substance use before it progresses to addiction. Further, the physician will be better equipped to make the often difficult decision of when to prescribe opioids for at-risk patients with chronic nonmalignant pain.

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Introduction

Substance dependence (addiction, as opposed to only physical dependence) criteria in the *Diagnostic and Statistical Manual of Mental Disorders* include a maladaptive pattern of euphoria producing substance use over a 12-month period, with clinically significant impairment or distress, manifested by three or more of seven criteria (Table 1).¹ Five of these criteria emphasize a state of compulsive use and loss of control over substance use despite adverse consequences of use, which constitute the essential features of addiction. Substance abuse involves continuing use without loss of control despite fewer consequences of use. For the purpose of this review the term *addictive disorders* (ADs) refers to substance dependence to drugs including alcohol. Although about 15% to 30% of patients in primary care and nearly 50% of patients with psychiatric illnesses are affected, these patients who have ADs often remain undiagnosed and untreated.² Addiction to alcohol or other drugs is often viewed in our society as a voluntary behavior problem by the morally corrupt. However, an increasing body of evidence is now demonstrating that addiction is a brain disease with numerous factors that likely predispose individuals to be more susceptible to these disorders. Initiation of alcohol and

drug use peaks in adolescence and declines after adulthood.³ Therefore, much research has been focused on the major risks for ADs in the younger age group. These factors outlined in a review by Hawkins et al. include those of the environment and of the individual.⁴ This paper will discuss the major risk factors for AD (Table 2) including those of the environment that are more likely to affect initiation of use, and those genetic factors of the individual more likely to affect progression to addiction.⁵ An understanding of these risk factors will help the physician to assist those at risk for addiction by:

1. preventing the initial use of substances of abuse,
2. slowing or stopping progression toward addiction, and
3. avoiding or limiting the use of potentially addictive substances such as opioids for chronic nonmalignant pain.

The environment

Family environmental factors include parental use, family permissiveness, inconsistent parenting, and childhood abuse and neglect.⁶ Several studies support parental and sibling use as promoting the initiation of drug and alcohol use in adolescents. However, parental permissiveness was found to be an even more significant factor.⁴ Inconsistent discipline, negative communication, and an unrewarding family

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Table 1 DSM-IV dependence (addiction) criteria

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. tolerance, as defined by either of the following:
 - a need for markedly increased amounts of the substance to achieve intoxication or desired effect markedly diminished with continued use of the same amount of substance
2. withdrawal, as manifested by either of the following:
 - the characteristic withdrawal syndrome for the substance
 - the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
3. the substance is often taken in larger amounts or over a longer period than was intended
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use
5. a great deal of time is spent in activities to obtain the substance, use the substance, or recover from its effects
6. important social, occupational, or recreational activities are given up or reduced because of substance use
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Information adapted from the American Psychiatric Association (2000).¹

environment were associated with increased drug use, whereas parent-child bonding, family rules, monitoring and attachment, and maternal stability, including interaction with their children, were found to be protective.^{4,7} Several adverse childhood events (ACEs) and subsequent illicit drug use were studied by Dube et al.⁸ They found approximately double the probability of illicit drug use initiation after emotional abuse (O.R. 2.1), physical abuse (O.R. 2.0), sexual abuse (O.R. 2.0), and neglect (O.R. 1.8). Further, with five or more ACEs, the odds ratios of “ever having a drug problem” and “drug addiction” were 12.0 and 9.2, respectively.⁸ Bulik et al. found the probability of addiction to alcohol and drugs, respectively, increased significantly after intercourse alone (O.R. 1.6 and 2.4), if threat or force was involved (O.R. 1.5 and 2.2), and especially if a negative response was obtained when the sexual abuse was reported to another person (O.R. 2.2 and 3.6).⁹ Thus, familial environmental factors can significantly increase the risk for subsequent addiction or be protective.

Societal factors that affect addiction include advertising and taxing of legal drugs (alcohol, cigarettes), interdiction, and availability. The review previously cited on risk and protective factors for alcohol and drug use by Hawkins et al. reported that taxation decreased alcohol use, whereas availability increased the use of alcohol and illicit drugs and that exposure to advertising increased alcohol use.⁴ Advertising has been shown to increase consumption of alcohol by teens and young adults. Exposure to one advertisement has been shown to result in a 1% increase in consumption over the previous month (current use).¹⁰ An increase in taxation of alcohol has been shown to result in a decrease in decisions to drink, as well as total alcohol consumption.¹¹

However, a doubling of interdiction and increased arrests of drug dealers has not been found to increase illicit drug prices or decrease drug availability.⁴ Thus, although government policy focuses on limiting the availability of drugs, according to Jonas, “the drug war has not only consistently failed to meet its own stated objectives but its very nature

cannot in any way be successful in dealing with the drug problem because of its totally distorted focus.”¹² Societal factors therefore appear to have a mixed association with ADs. Although advertising increases and taxation decreases use of legal substances, interdiction and criminal sanctions appear to have little effect on illicit drug use.

Other environmental factors include social status, poverty, neighborhood, peers, and school. Low socioeconomic status and extreme poverty are factors associated with drug use in adolescents, childhood antisocial behavior, and subsequent alcohol and drug use in adulthood.⁴ According to Winstanley et al., “disorganization of the neighborhood” has been found to be linearly and positively associated (odds ratios 1.14-2.60) with adolescent drug use and dependence.¹³ Antisocial peer influence has been found to be a high predictor of initiating substance abuse, whereas family rules, monitoring, and attachment were found to be protective.⁷ Several studies have shown that peer influence is the most significant factor favoring the initiation of drug use, with more impact than parental protective effects in white, African American, Asian, and Hispanic adolescents.⁴ Plans to attend college, “liking school,” and good school performance have been associated with decreased drug use in adolescents, whereas peer rejection in elementary school, truancy, and school failure are associated with more drug use.⁴

The individual

Much evidence suggests that child and adolescent mental health problems are associated and coexist with ADs.¹⁴ These psychiatric disorders are commonly viewed as externalizing behaviors such as conduct disorder, delinquency, aggression, and attention deficit–hyperactivity disorder (ADHD), and internalizing problems including anxiety and depression. As many as 50% of those with ADs have been identified as also having ADHD.^{15,16} A recent study found

Table 2 Risk and protective factors of addiction

Risk factors	
Family	
	Parental/sibling use
	Parental permissiveness
	Inconsistent discipline
	Emotional abuse
	Physical abuse
	Sexual abuse
	Neglect
Neighborhood	
	Poverty
	Antisocial peer group
	Peer use
School	
	Elementary school peer rejection
	Truancy
	School failure
Individual	
	Family history addiction
	Male gender
	Conduct disorder
	Delinquency
	Aggression
	Attention deficit–hyperactivity disorder (ADHD)
	Depression
	Anxiety
Protective factors from addiction	
	Maternal stability
	Parent-child bonding
	Family rules
	Parental monitoring
	Liking school
	Good school performance
	Plans to attend college
	Taxation

delinquent behavior to have a strong relationship with ADs and little association with internalizing problems (anxiety and depression).¹⁴ Gau et al. found the highest of seven potential predictors of ADs to be male gender, conduct disorder, and ADHD, with little correlation to anxiety and depression.¹⁷ Ferdinand found in a longitudinal study that male gender, thought problems, and delinquent behavior were associated with tobacco, alcohol, and drug use.¹⁸ Further, adolescents with serious delinquent behavior have been reported to initiate cocaine use nearly twice as often as nonserious delinquents.¹⁹ Thus, externalizing behaviors including conduct disorder, delinquency, aggression, and ADHD are associated with AD, whereas the association with internalizing problems including anxiety and depression is less clear.

The brain and addiction

Two major brain areas are involved in balancing “go” and “stop” in addiction. First, the mesolimbic dopamine path-

way (MDP) consists of dopamine cell bodies located in the ventral tegmental area, which project to the nucleus accumbens (Nac) and other midbrain areas.²⁰ This “go” pathway provides reward or wanting of a prospective reward from natural stimuli such as food, sex, or social reinforcement. Drugs of abuse directly or indirectly highly overstimulate and alter the MDP, with down-regulation of dopamine receptors.²⁰ The result is an extreme learned drive for drugs or alcohol despite both decreasing pleasure from their use and an overall anhedonia.

Second are the prefrontal cortex (PFC) “executive” areas, where we evaluate options and their consequences, choose appropriate actions, and suppress inappropriate previously rewarded responses to change behavior.²⁰ Drugs of abuse can also alter this decision-making area, resulting in impairment of these “stop” signals. An unchecked “go” pathway results in uncontrolled compulsive use of drugs “to the exclusion of alternative goals and in the face of familial, social and medical problems.”²¹ This imbalance in neural function is the very definition of addiction.

Genetic factors

A high concordance rate has been demonstrated in monozygotic vs. dizygotic twin pairs for alcoholism, illicit drugs, and smoking initiation. Genetic influences for females and males accounted for 47% and 79%, respectively, of the differences between identical and fraternal twins in abuse, dependence, or both for any drug.²² Dopamine receptors play a primary role in the MDP, and subjects with alleles resulting in a decreased quantity of D2 receptors demonstrate a heightened severity of alcoholism, consume greater quantities of alcohol, and initiate problem drinking at an earlier age.²³ Further, Saxon et al. reported a “vulnerability for both opioid and cocaine dependence” because of inherited polymorphisms in genes coding for dopamine receptors, dopamine transporter, opioid receptors, endogenous opioid peptides, cannabinoid receptors, serotonin receptors, and serotonin transporter.²⁴ Subjects with a genetically determined decreased quantity of D2 receptors in the Nac, PFC, hippocampus, orbital frontal gyrus, and midbrain “may compensate for the deficiency of their dopaminergic system by the use of alcohol and other substances.”²⁵ Thus, Comings and Blum suggest that drug addiction may result from a “reward deficiency syndrome,” putting individuals at increased risk for abuse of unnatural rewards.²⁶

Genetic and environment interaction

Genetic and common psychiatric and environmental risk factors were examined in twin pairs by Kendler et al.²⁷ The highest odds ratios for comorbid alcohol dependence were with major depression, adult antisocial behavior, and conduct disorder, whereas those for comorbid drug addiction

was with adult antisocial behavior and conduct disorder. Conduct disorder and adult antisocial behavior were also shown to be environmentally influenced.²⁷ These behaviors may both have common environmental and genetic etiologies; Doherty et al. also reported that delinquents with 28% to 29% early substance abuse came from backgrounds of poverty (56%), female head of family (38%–44%), and family substance abuse (16%–20%).¹⁹ Thus, genetic studies support previously found associations of externalizing behaviors and may help clarify internalizing behavior associations with ADs.

Childhood neglect, physical abuse, sexual abuse, and/or emotional abuse have been shown by De Bellis et al. to chronically alter levels of cortisol and norepinephrine, with resulting maturation failures in frontal and PFC brain areas. These deficits result in impairment of decision-making and self-regulation, including the promotion of impulsive behavior.²⁸ Thus, an adolescent may be predisposed to future drug use and ADs because of a developmentally altered brain functioning caused by known environmental factors. A common, genetically determined failure of behavioral inhibition may lead to both the behaviors associated with ADHD and the initiation and progression of ADs.²⁹

Conclusion

Multiple environmental risk factors are associated with the initiation of potentially addictive drugs, with peer influence playing an especially significant role, whereas risks for subsequent progression to addiction appear to be primarily those of the individual. Environmental risks include those of the family and society. Factors of the individual include coexisting mental disorders (e.g., conduct disorder, delinquency, ADHD), genetic makeup, and male gender. However, it is the interaction of genetic and environmental factors, including stress-related changes in brain function, that appear most significant in the risk for addiction. Although environmental factors heavily influence the initiation of drug and alcohol use, the genetic makeup of the individual appears to not only influence progression toward addiction, but also predisposes one to initiate use. An enhanced understanding of these risk factors will help the physician to counsel those at risk to avoid the initial use, slow, or stop substance use before it progresses to addiction.

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1.c, 2.b, 3.d, 4.d, 5.d, 6.a, 7.c, 8.b, 9.a, 10.b