Risk and Protective Factors for Alcohol Abuse and Dependence

Substance Abuse and Addiction

Rather than a focus on drug withdrawal, alcohol and other substances of abuse are defined by self-administration in lab animals and man. All drugs of abuse affect the brain's reward pathways. Drugs of abuse stimulate their own taking and change the organism's appreciation of pleasure and motivational hierarchies. While some drugs have a specific, single brain receptor or transmitter target, like opiates, alcohol has a more widespread and general effect. Alcohol, food and dugs of abuse have similar effects on dopamine receptors. But a focus on dopamine does not tell the whole alcohol story. The effects of alcohol appear to be related to complex multiple interactions with the dopamine, GABA, serotonin, opioid, and NMDA neurotransmitter systems. The effects of alcohol on these neurotransmitters are described under Alcohol and the Brain. New data is suggesting that the reinforcing effect of alcohol is also partially mediated through nicotinic receptors in the ventral tegmental area, which when combined with nicotine, may be a factor in the high incidence of smoking among those who are alcohol dependent (Tizabi et al. 2002). There are several theories of addiction, influenced by genetics**,** psychological and social/environmental risk factors.

One theory is that dependence risk is inherited by alterations in the rewarding chemicals released per dose of alcohol, which is described further under Alcohol and Genetics. Recent events, such as the September 11th terrorist attacks, have prompted researchers to expand what is known about the relationship between alcohol use and stress, trauma and Post Traumatic Stress Disorder (PTSD). Our work with physician addicts have emphasized the importance of age of onset since even physician addicts who have a very high rate of success in alcohol

treatment have the best outcomes when drinking starts later in life (Hall et al, 2002). Studies are also reporting protective factors for substance abuse and dependence.

Alcohol and the Brain

Alcohol affects most neurochemical systems including NMDA, GABA, serotonin, dopamine, and opioid systems.

Dopamine (DA): Alcohol activates DA in the reward system in the ventral tegmental area of the brain. Alcohol also causes the release of DA. Several DA receptors may be may be related to the genetic risk of alcohol dependence (Schuckit 2000, and Schuckit 2002).

Serotonin (5HT): Alcohol causes the release of 5-HT. Lower 5-HT levels in the brain is associated with increased alcohol intake in animals and humans, while higher 5-HT levels are associated with slightly reduced alcohol intake. Several 5-HT genes may be related to the genetic risk of alcohol dependence (Schuckit 2000, and Schuckit 2002).

N-methyl-D aspartate (NMDA): Alcohol inhibits NMDA systems and which may contribute to felling intoxicated. NMDA receptors change as tolerance develops. These receptor systems are overactive during withdrawal.

Gamma aminobutyric acid (GABA): Alcohol enhances the action of the GABA system producing some of the symptoms of acute intoxication. $GABA_A$ receptors are especially sensitive to alcohol. The GABA system is under active during withdrawal and the genes that control these receptors may impact on the risk of alcohol dependence (Schuckit et al. 1999).

Opioid System: Alcohol causes the release of endogenous opioids and opioid receptors change with tolerance and withdrawal. Some receptors may affect genetic predisposition for alcohol dependence and opioid antagonists can decrease voluntary alcohol consumption. Alcohol may also affect acetylcholine, norrepinephrine and steroids.

Alcohol and Genetics

Research has shown that genetic factors play a strong role in whether a person becomes an alcoholic, accounting for 40-60% of the risk (Kendler et al 1997, Schuckit 2002). In fact, family transmission of alcohol dependence has been well established. Individuals who have alcoholic relatives are at 3 to 5 times greater risk of developing alcohol dependence than the general population. The presence of alcohol dependence in one or both biologic parents is more important than the presence of alcohol dependence in one or both adoptive parents. The genetic risk of alcohol dependence increases with the number of alcoholic relatives and the closeness of the genetic relationship (Schuckit 2002). However, most children of alcoholics do not become alcoholics themselves, and some children from families where alcohol is not a problem develop alcohol dependence when they grow up. Alcohol dependence is seen in twins from alcoholic parents even when brought up in environments where there is no or little drinking. Identical twins adopted into households with an alcoholic step father do not show more alcohol dependence than the general population, while children with close biological relatives who are alcoholic adopted into a never drinking, even religiously opposed family can readily develop alcohol problems. Thus, there are many factors-- psychological, social, environmental, and genetic -- that determine whether a person develops alcohol dependence.

As mentioned previously, genetic factors are thought to account for 40-60% of the risk of developing alcohol dependence (Kendler et al, 1997, Schuchit 2002). Animal studies have shown that genetic factors may be responsible for enhanced brain reward produced by alcohol, decreased initial impairment, or even altered metabolism of alcohol (Hwang et al., 1999, Risinger et al., 1999, Roberts et al., 2000, Thiele et al., 1998, Bowers et al., 1999, Yagi et al., 2000, and Engel and Allan, 1999).

Genetic factors appear to influence the level of response (LR) to alcohol as measured by the intensity with which one reacts to a given quantity of alcohol (Schuckit, 1998). The level of response to alcohol varies from individual to individual depending on the tolerance. Low LR at and early age contributes to the risk of alcohol dependence later in life (Schuckit 1998, Krystal 2002).

Genetic differences in metabolic or other biological processes may play a role in the development of alcohol dependence in specific individuals. Studies using a self-rated scale have shown consistent results of sons of alcoholic fathers scoring themselves lower than sons of non-alcoholic fathers on feelings of drunkenness, dizziness, drug effect, and sleepiness following alcohol consumption (Shuckit and Smith, 2000). This suggests that sons of alcoholic fathers have a less intense reaction to alcohol than sons of non-alcoholic fathers. Understanding reactions to alcohol could establish a better understanding of future risk of developing alcohol dependence in these men. High alcohol sensitivity in men is associated with substantially decreased risk of alcohol dependence. Decreased alcohol sensitivity identifies twins and males at the highest risk of alcohol dependence.

More recent studies have found similar results of higher tolerance for alcohol among daughters of alcoholics. One study examined the drinking patterns of 38 daughters of alcoholics compared with 75 family-history-positive men (FHP men) from the same families and 68 men with no family history of alcohol dependence (family-history-negative/FHN men) (Schuckit et al., 2000a). FHP men and women reacted in the same way with low reaction to alcohol. This indicates that the degree of genetic influence on alcohol related behavior is similar for both for men and women with family history of alcohol dependence. In a study of adolescent and young adult offspring from families where alcohol dependence is prevalent, researchers found both neurophysiological and neuroanatomical differences, such as reduced right amygdala volume, when comparing these offspring to controls (Hill et al. 2001).

Low response levels are associated with increased risk of dependence. Certain groups are more likely to have a lower of response to alcohol. About 40% of children of alcoholics have significantly lower levels of response. American Indians also have a lower level of response and an increased risk of alcohol dependence. (Schuckit 2002). High levels of impulsivity/sensations seeking/disinhibition are also genetically influenced and may impact alcohol dependence risk (Schuckit 2002).

The alcohol metabolizing enzymes are another important genetic influence especially for persons of Asian decent (Schuckit 2002). About 50% of Japanese, Chinese and Korean persons flush and have a more intense response to alcohol because they have a form of aldehyde dehydronase that causes high levels of acetaldehyde. About 20% of the Jewish

population also has the allele of the alcohol dehydronase 2 (ADH2) gene that protects against alcoholism (Hasin et al. 2002). This ADH2*2 allele was found to be protective against the severity of dependence in a recent study (Hasin et al. 2002). Forms of aldehyde dehydronase contribute to a higher rate of alcohol metabolism, intensify the response to alcohol, and lower this risk of alcohol dependence.

Alcohol Initiation, Polysubstance Use, and Risk of Abuse and Dependence

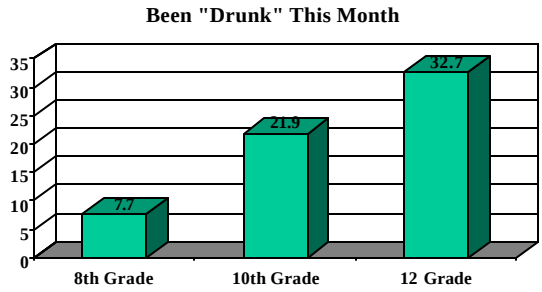
Substance use at an early age increases the risk of dependence. The Center on Addiction and Substance Abuse reports that the risk of substance abuse increases by almost 500 percent between the ages of 12 and 16 (CASA). For alcohol, the mean age of initiation is 12.5 years, and 93% of teens who consume alcohol start drinking by the time they are 15 years old. (CASA 2002). Tobacco use is generally initiated at a slightly younger age than alcohol, yet they are commonly used together. Children who smoke and drink have a substantially greater risk of other drug use.

The Monitoring the Future survey tracks drug and alcohol use patterns among 8^{th}, 10^{th} and 12^{th} graders (Johnston et al. 2002). The percentage of students reporting being "drunk" in the last month is reported in figure 1. The risk of alcohol dependence is 4 times greater among persons who start drinking before age 15. While alcohol dependence can develop at any age, repeated intoxication at an early age increases the risk of developing an alcohol use disorder (Schuckit 2000). Usually dependence develops in the mid twenties through age forty. Alcohol abuse is extremely amenable to brief intervention, but our data suggests that physicians may not be prepared to talk about

alcohol issues with their patients (Gold et al. 2002). Without intervention, 10% of those who abuse alcohol will likely progress to dependence and 50% to 60% will continue to experience problems over the next 5 years (Schuckit et al. 2001).

Figure 1.

2001 Monitoring the Future Survey



Johnston et al., 2002

Psychological and Social/Environmental Risk Factors

Researchers who study risk factors have developed "models" of the ways that known risk factors may interact to create pathways to alcohol dependence.

Three Models of Risk Factors

Children With Conduct Problems: One model focuses on children who have temperaments that make it difficult for them to regulate their emotions and control their impulses. Clearly, these children are difficult to parent, and if one or both of their parents are alcoholics, it is likely that they will be poorly socialized and have trouble getting along in school (Cadoret et al. 1995). Poor academic performance and rejection by more mainstream peers at school may make it more likely for these children to join peer groups where drinking and other risky behaviors are encouraged. If the parents are alcoholics, it is likely they will not monitor these

children closely and will lose control over them at an early age. These children will begin drinking early, often before the age of 15 (Grant et al. 2001). If such a child is already carrying the genes that predispose toward alcohol dependence (Goodwin 1974), these environmental factors additionally increase the tendency toward alcohol dependence.

Stress and Distress: Another model of a pathway of risk factors leading to alcohol dependence focuses on drinking to regulate inner distress (Conrod et al. 1995). Some children have temperaments that make them highly reactive to stress and disruption. This type of child may be born into an alcoholic family, where the stressors may be intense, or a nonalcoholic family, with everyday types of low-level stressors. No matter which type of family these children find themselves in, they maintain higher levels of inner distress (anxious and depressed feelings) than other children. When they take their first drink, the inner distress dissipates for awhile, which leads to more and more drinking and may lead to alcohol dependence. Some recovering alcoholics report that the first time they drank was the first time they felt like themselves.

However, for some individuals, at certain doses, alcohol may induce rather than reduce the stress response. Alcohol can actually induce the stress response by stimulating hormone release by the hypothalamus, pituitary, and adrenal glands (Soderpalm and DeWit 2002). Alcohol may be more rewarding when taken under duress, extreme trauma or inescapable stress. Alcohol is rewarding when taken in any situation but stress appears to make it even more rewarding and dependency producing. More research is needed before we understand

the exact role of stress as a risk factor in alcohol dependence. However, stress is a critical factor in terms of relapse (Liu and Weiss 2002).

Sensitivity to Alcohol's Effects: A third risk factor model focuses on sensitivity to the effects of alcohol—both to its sedative properties and its stimulating qualities (Volavka et al. 1996). The stimulant-like (increased heart rate and blood pressure) and sedative properties (such as impaired vigilance and psychomotor performance), depend on the quantity of alcohol consumed, the time elapsed since consumption, and individual differences in response (Holdstock and deWit 2001,1998). Volavka and colleagues found that low EEG response to small amounts of alcohol may be associated with future development of alcohol dependence (1996). In a recent study, heavy drinkers had less sedation and cortisol response after alcohol consumption than light drinkers (King et al. 2002). In addition, heavy drinkers were more sensitive to the positive stimulant-like properties as blood alcohol levels increased (King et al. 2002).

Known Risk Factors for Alcohol dependence

With these interactive models in mind, a quick review of some of the research findings on genetic and psychosocial risk factors may provide a better understanding of the factors leading to alcohol dependence.

- **Temperament:** Moodiness, negativity, and provocativeness may lead to a child being criticized by teachers and parents. These strained parent-child interactions may increase the chances that a child will drink.

- **Hyperactivity:** Hyperactivity in childhood is a risk factor for the development of adult alcohol dependence. Children with ADHD and conduct disorders have increased risk of developing an alcohol use disorder (Sullivan and Rudnik-Levin 2002). Childhood aggression also may predict adult alcohol abuse.
- **Parents:** The most compelling and large body of research shows parents to be the most important factor in an adolescent's decision to drink. A recent survey found that parents and siblings influence whether or not teens drink, smoke or use other drugs (CASA, 2002).
- **Gender:** Among adults heavy alcohol use is almost three times more common among men than women and also more common among males in middle or high school than among females. Males with ADHD and/or conduct disorders are more likely to use alcohol than males without these disorders, while females who experience more depression, anxiety, and social avoidance as children are more likely to begin using alcohol as teens than females who do not experience these negative states.

Bipolar disorder, schizophenia, antisocial personality disorder, and panic disorder all increase the risk of a future alcohol use disorder (Schuckit 2000).

Abuse and Adverse Conditions in the Home:

Childhood abuse is a significant risk factor for later alcohol and substance abuse (Schuck and Widom 2001). Women who were physically abused are 1.5- 2 times more likely to abuse alcohol than non-abused adults. Children from crowded, noisy, and disorderly homes without rules or religion are more likely to abuse alcohol as teens. Children who are

quick to anger, who perceive themselves to be highly stressed, who are resentful of parents' absences, or who have repeated conflicts at home are more likely to abuse alcohol as teens.

Disasters, the Events of 9/11, Terrorism and Alcohol Use

Disasters have a significant impact on mental health. Anxiety and panic disorders, depression and Post Traumatic Stress Disorder are just some of the commonly documented psychological consequences of these horrific events (Smith et al. 1990). Studies since September 11th have shown high levels of stress, depression and PTSD in New York and throughout the US (Galea et al. 2002 and Schuster et al. 2002). Recently published results of a telephone survey of Manhattan residents compared alcohol, cigarettes, and marijuana use prior to and after September 11th(Vlahov et al. 2002). Use of all three substances increased. Of those who consumed alcohol prior to the terrorist attacks, 41.7% increased the frequency of alcohol consumption and 20.8% reported consuming one or more extra drinks per day. In this study, increased alcohol consumption was associated with current depression but not current PTSD. The authors suggest that alcohol use may be an important factor in terms of PTSD in the medium to long-term (Vlahov et al. 2002).

Trauma, Stress and Post-Traumatic Stress Disorder (PTSD)

Symptoms of PTSD may include reexperiencing the trauma; avoiding people, places, and thoughts associated with the event; and arousal, which may include exaggerated startle response, hypervigilance and trouble sleeping. People who have these symptoms may use drugs and alcohol to self-medicate to escape these realities (Khantzian 1985, Chilcoat et al.

1998). One study of adolescent psychiatric inpatients found that 93% had been exposed to one or more traumatic events and 32% met diagnostic criteria for current PTSD (Lipschitz 1999). Research has shown high rates of PTSD and Substance Use Disorder comorbidity. In one study, 75% of veterans with combat related PTSD also met alcohol abuse or dependence criteria (Kulka et al. 1990). In the general population, rates of drug abuse and dependence are much higher among persons with a history of PTSD. 34.5% of males and 26.9% of females with a history of PTSD had a lifetime history of drug abuse and dependence, compared 7.8% of males and 7.6% of females without PTSD (Kessler et al. 1995). In men who have a lifetime history of PTSD, rates of comorbid alcohol abuse or dependence are highest, while in women rates of comorbid depression, and some anxiety disorders are highest followed by alcohol abuse and dependence (Kessler et al. 1995). In a community based study of 15 to 19 year olds, rates of PTSD ranged from 6.3% in the general sample to almost 30% among substance dependent teens (Giaconia et al. 1995). Another study found reported a PTSD prevalence of 19.2% among chemically dependent teens (Deykin and Buka 1995).

Substance Use Disorders and PTSD occur together frequently, suggesting that the two are related (Jacobsen et al 2001). Substance abuse and dependence, particularly on CNS depressants, is common in patients with PTSD. In general, the onset of PTSD is thought to precede the onset of substance abuse and dependence (Saxon et al. 2001). In a study designed to explore the relationship between PTSD and substance abuse and dependence, researchers found that persons with PTSD had a 4 times greater risk of Substance Use Disorders (Chilcoat et al. 1998). Research suggests that patients with PTSD have lower benzodiazapine receptor binding in the prefrontal cortex, which may bring about symptoms of PTSD (Bremner et al. 2000). Again, persons with PTSD may be self-medicating to relieve their symptoms.

Volpicelli and colleagues suggest that people may use alcohol to compensate for decreased endorphin activity following trauma (1999). Endorphins help to numb the pain of trauma during the experience, but levels decrease after the trauma and can lead an endorphin withdrawal (Volpicelli et al. 1999). Because drinking increases endorphins, persons may drink to avoid endorphin withdrawal and to ease the psychological distress of trauma (Volpicelli et al. 1999).

For many reasons, PTSD is hard to prevent. Usually, we do not know when or where disasters will happen, terrorists will attack, or when individuals or groups will be victimized or witness violent/traumatic events. In addition, different people may have different reactions to the same event, so there is individual variation in the development of PTSD. It is important that those who have PTSD, receive appropriate treatment and that substance use is assessed and monitored. Since comorbidity is high, it is also important that persons with a substance use disorder be evaluated for PTSD.

Protective Factors

An exciting area of research is currently focused on protective factors: instead of asking, What makes a child grow up to be an alcohol dependent? The question becomes, What protects children from taking one of the risk pathways to alcohol dependence? Some potential protective factors are listed in table 1.

Table 1. Protective Factors for Adolescents

- Teens who are very "connected" to their parents
- Increased parental presence in the home
- High self-esteem
- Personal importance placed on religion and prayer
- Few nights out with peers

- Disapproval and avoidance of peers who drink
- Student focus on school and grades
- High levels of school "connectedness"

In 1997, some good news came from the National Longitudinal Study on Adolescent Health, a survey in which nearly 12,000 students in grades 7 through 12 were given lengthy interviews timed one year apart. The researchers were trying to determine what kept children over the course of that year from taking health risks in four areas—substance abuse (cigarettes, alcohol, and marijuana), sexuality, violence, and emotional health (Resnick et al. 1997). The researchers found two factors that protected these children in all four areas. They named the factors: Parent-Family Connectedness and School Connectedness.

Children identified as having Parent-Family Connectedness said they felt close to their mother or father, they felt that their mother or father cared about them, they felt satisfied with their relationship with their mother or father, and felt loved by family members (Resnick et al. 1997). School Connectedness was experienced as a feeling of being part of one's school and a belief that students were treated fairly by the teachers.

Conclusions

Alcohol abuse and dependence affects millions of Americans; those suffering from the disease, their families and friends, victims of alcohol related accidents and crimes, and society, which bears a huge economic burden. Risk factors for alcohol dependence include but are in no way limited to genes. Family history of alcohol dependence, twin data for alcohol

dependence and recent neuroimaging studies have focused attention on the important role of genes in risk. The recent tragic events surrounding 9-11 have underscored the role of trauma, inescapable stress, depression and other "environmental factors" in risk of abuse and dependence. Identification of risk factors can help people be aware of their individual risk. Persons with known risk factors could benefit from prevention and early intervention services.

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CME Questions

1. Which of the following is not true about persons with low response levels to alcohol?
    a. they have a lower risk of alcohol dependence
    b. they have a higher risk of alcohol dependence
    c. low response levels are influenced by genetic factors
    d. men and women with a family history of alcohol dependence are more likely to have low response levels

2. The effects of alcohol appear to be related to complex multiple interactions with which of the following neurotransmitter systems
    a. dopamine and serotonin
    b. opioid and NMDA
    c. GABA
    d. All of the above
    e. None of the above

3. For alcohol, the mean age of initiation is 12.5 years. How does early drinking influence risk of alcohol dependence?
    a. it does not impact risk of dependence, because dependence usually does not develop until the mid-twenties through forty.
    b. experimentation is common, but kids grow out of it by the time they are young adults
    c. people who start drinking before age 15 have a four times greater risk of alcohol dependence
    d. children who use alcohol and tobacco are more likely to try other drugs of abuse

4. Which of the following has been established regarding the relationship between alcohol and stress?
    a. alcohol can induce the stress response by stimulating hormone release by the hypothalamus, pituitary and adrenal glands
    b. alcohol may be more rewarding and dependency producing when taken under duress, extreme trauma or inescapable stress.
    c. Alcohol and other Substance Use Disorders commonly occur together with PTSD, suggesting the two are related.
    d. In general the onset of PTSD is thought to precede the onset of substance abuse and dependence
    e. All of the above

5. Which of the following is NOT a protective factor for alcohol dependence?
    a. parent-family connectedness
    b. school connectedness
    c. peer connectedness
    d. personal importance placed on religion and prayer