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Drug Abuse Heterogeneity and the Search for Subtypes

Meyer D. Glantz, Kevin P. Conway
and James D. Colliver

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1. SUBSTANCE ABUSE AND HETEROGENEITY

Progress in treating health problems is often made by determining the critical commonalities and differences among the phenomena of interest, using observations to discriminate subtypes, and then determining the underlying mechanisms and etiologies of the subtypes. These causal attributions typically become the distinguishing principles on which the sub-categories are based. When the identified subtypes indicate varying etiological factors, there may be varying subtype-specific indicated interventions. In such cases, differential diagnosis then becomes a primary step in formulating optimal treatment. The benefits of specifying the subtypes

MEYER D. GLANTZ, KEVIN P. CONWAY AND JAMES D. COLLIVER • Division of Epidemiology, Services and Prevention Research, National Institute on Drug Abuse, National Institutes of Health

of disorders are clear (Glantz and Colliver, 2002). It is much like the difference between selecting a treatment for someone knowing only that they have some condition involving nasal congestion versus selecting a treatment knowing whether they have a cold, the flu, allergies, or a sinus infection. A differential diagnosis would not only improve treatment effectiveness, but it might also help the patient to prevent future episodes by using the information about his or her susceptibilities.

The differentiation of subtypes of psychiatric disorders or the disaggregation of pathological conditions into distinct clinical entities has been an essential step in improving diagnosis and treatment. For example, the delineation of Attention Deficit Disorder (ADD) and in particular its distinction from both a general lack of intellectual aptitude and from willful opposition or laziness has been a major accomplishment. Further differentiation of ADD from ADD co-occurring with Conduct Disorder is also proving to be valuable. Examinations of heterogeneity and subtypes are a central goal in these and other areas of psychopathology research (e.g. McKay et al., 2004; Grilo, Masheb and Wilson, 2001; Spence, 1997). However, the questions as to the extent to which substance abuse is heterogeneous and what is the nature of that heterogeneity are not only unanswered but are often not even addressed.

This is not to suggest that aspects of substance abuse heterogeneity are not recognized. For example, there is no disagreement that people abuse different substances and this is a key factor in their differential diagnosis under the major diagnostic systems, the *Diagnostic and Statistical Manual of Mental Disorders*, (DSM), (APA, 1994) and the *International Classification of Diseases* (ICD), (WHO, 1993). However, there is no consensus about the relationship of these disorder subtypes to each other. For example, there is no consensus on whether alcohol, tobacco, cocaine and heroin dependence are fundamentally the same disorder except for the substance being abused, its legal status, and its physical effects. The other major diagnostic distinction in DSM and ICD relates to the categories of "abuse" and "dependence" for each of the substances covered. Regardless of the distinctions of substance and level of disorder, these diagnostic subcategories serve few of the explanatory or directive functions of fully delineated clinical entities or subtypes.

The issues grow even more complicated given that some researchers hypothesize that substance use disorders arise from common underlying neurochemical systems and responses (e.g. Hyman and Nestler, 1996; Koob and Le Moal, 1997), and others hypothesize that there are common underlying genetic predispositions (e.g. Tsuang et al., 1998; Kendler et al., 2003). There is general agreement that substance abusers are heterogeneous in terms of the drugs they use and the routes of administration, whether they have serious practical and/or psychiatric problems associated with their drug abuse, and whether they are physically (and possibly psychologically) dependent on the drugs they abuse. There is also agreement that abusers often use different drugs at any given time and over time and that they

may follow varying patterns of abuse behavior such as having different ages of onset and different patterns of escalation. These observations have not led to any fundamental subcategorization of substance abuse into heuristically useful and distinct clinical entities and there is a tacit assumption of basic underlying homogeneity. Perhaps as a result, the selection of differential treatment is largely based on pharmacological factors and environmental features (such as the legal status of the abused drug) rather than conceptualizations of the fundamental processes involved in substance abuse behavior.

2. EPIDEMIOLOGY

In the general population of the United States 12 years of age and older, around 46 percent—an estimated 108 million individuals—have tried an illicit drug at least once in their lives according to the 2002 National Survey of Drug Use and Health (NSDUH, formerly known as the National Household Survey on Drug Abuse; SAMHSA 2003). Forty percent have tried marijuana and 30 percent have used illicit drugs other than marijuana. Lifetime use of alcohol and tobacco is much higher, with 83 percent indicating they have used alcohol and 73 percent reporting use of tobacco products. One in seven (14 percent) have used cocaine and a similar proportion have tried hallucinogens. One-fifth report having used a prescription-type psychopharmaceutical drug (analgesic, tranquilizer, stimulant or sedative) when they did not have a prescription for it or just for the feeling or experience they expected it would provide. Research has consistently shown that the large majority of those who use drugs do not escalate to substance abuse or dependence (using DSM-IV criteria) suggesting that while the early substance use behaviors may be the same for both those who will and those who will not eventually develop a substance use disorder, the underlying processes may be heterogeneous (Haertzen, Kocher, and Miyasato, 1983; Pomerleau, Pomerleau, Namenek, and Marks, 1999).

Differing patterns of onset and escalation may also be indicative of divergent patterns or subtypes. Individuals who start using drugs early in life are at increased risk of progressing to more serious drugs and of developing drug use disorders (Kandel and Yamaguchi, 1993; Robins and Przybeck, 1985; Anthony and Petronis, 1995; Grant and Dawson, 1998; Lynskey, 2003).

While it cannot be conclusively determined whether early onset, as distinct from correlated factors, accounts for this association, the number of young initiates of some drugs has been increasing in recent years (Figure 1). The top line in this graph shows an increase in new marijuana users who are under 18 years of age from 1990 to 1999, following a decline in the 1980s. New initiates into cocaine use, while not displaying a trend as dramatic as that for marijuana, were more numerous in 2000 than at the height of the cocaine epidemic of the mid-1980s.

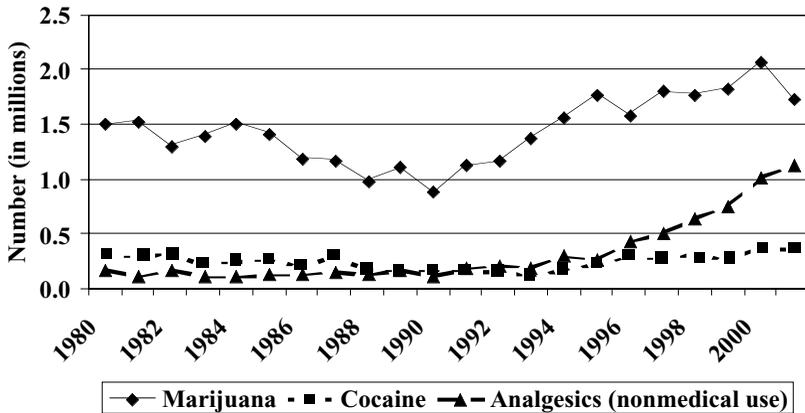


Figure 1. Number of initiates to drug use under age 18 by year and drug.

Of great concern is the recent increase in the number of new nonmedical users of prescription-type analgesics (e.g., oxycodone and hydrocodone).

Drug involvement increases not only through progression from one substance to another (e.g., cigarettes or alcohol to marijuana to other more illicit drugs) but also by escalation in the frequency of use of individual substances, shifts in the patterns and contexts of use, and development of substance abuse and dependence. Table 1 shows data on the frequency of marijuana use and rates of dependence among the estimated 26 million Americans who reported in 2002 that they had used the substance in the past year. Thirty-five percent used marijuana once a month or less, 36 percent used it more than 2 days a week, and 12 percent used it daily or almost daily (SAMHSA, 2003a). The likelihood of dependence on a drug increases with frequency of use. Among all past-year marijuana users, around 10 percent met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 1994) criteria for dependence on the drug in that time frame. As shown in Table 1, less than 5 percent of those who used marijuana two days a month or less often reported symptoms that met dependence criteria; among those using it daily or almost daily in the past year, however, 26 percent were dependent. Similar findings were reported by Grant and Pickering (1998).

The proportion of substance users who become dependent varies by drug. Estimates from the National Comorbidity Survey (NCS) indicated that 15 percent of lifetime alcohol users are dependent on alcohol at some time in their lives (Anthony et al., 1994). As shown in Figure 2, higher rates of lifetime dependence among lifetime users are found with tobacco (32 percent), heroin (23 percent), and cocaine (17 percent), while lower rates are observed with stimulants (11 percent), anxiolytics (9 percent), cannabis (9 percent), and analgesics (8 percent). These figures are for 1990–1992 and are based on individuals 15–54 years of age.

Table 1. Frequency of Marijuana Use and Its Association with Dependence: 2002

Days used in past year	Percent of past-year users	Percent meeting criteria for dependence in past year
1 to 12 days	34.5	0.3
12 to 24 days	11.9	4.2
25 to 50 days	7.5	10.6
51 to 100 days	10.0	11.3
101 to 200 days	14.5	15.3
201 to 300 days	9.7	23.8
301 to 365 days	11.8	26.2
Overall	100.0	10.2

Source: 2002 National Survey of Drug Use and Health, Substance Abuse and Mental Health Data Archives Online Data Analysis System.

Also part of the question of the relationship of substance use to abuse and dependence are the questions of whether, and under what conditions, substance use is effectively equivalent to sub-threshold abuse or dependence. Similar questions have been raised related to models of other psychopathologies and have led to advances in understanding those disorders (e.g. for a discussion on sub-threshold depression, see Cuijpers and Smit, 2004). Investigating the heterogeneity of substance use patterns might lead to improved identification of those likely to experience significant problems even if their substance use does not escalate as well as early identification of those at greatest risk for experiencing significant problems associated with substance use escalation.

Scientific recognition that use, abuse and dependence are not just points on a continuum has been important. It has led, for example, to research showing that the predisposing or risk factors for drug use are different than those for abuse,

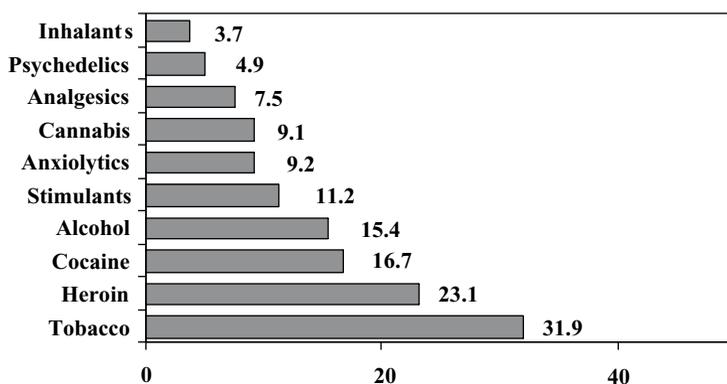


Figure 2. Rate of lifetime dependence among lifetime users 15 to 44 years old, by drug.

(Glantz and Pickens, 1992). Further investigations of the risk factors for substance use disorders might also help to explicate its heterogeneity and to suggest possible subtypes.

3. RISK FACTORS

Research has identified a wide range of risk factors for drug use and drug abuse (e.g. Hawkins et al., 1992) and some protective factors have also been identified. However, there have been few attempts to investigate these risk factors to determine if they group in meaningful clusters and to explore whether they are associated with subtypes of substance use disorders or even if they are specific only to substance use. Risk factors for substance use are often not distinguished from risk factors for substance use disorders, and it is often assumed that risk factors for substance involvement accumulate in a relatively linear fashion. While a greater number and severity of risk factors are likely to be associated with a higher-level risk and severity of outcome, different clusters of risk factors may have subtype related implications.

Evidence indicates that there are many paths to substance abuse. However, it is possible that the use of different drugs, differing patterns of drug onset, use and escalation, and/or different risk factors ultimately all converge to the same general substance abuse condition if the case is sufficiently severe. Such a common substance abuse outcome would be an instance of equifinality and if this were the case, then variations in the contributing factors and developmental course might have fewer implications for prevention and differential intervention. Alternatively, if variations in the paths of substance use lead to significantly different subtypes of substance abuse, then distinguishing major variations in etiological factors and patterns would have a wide range of heuristic and intervention implications. If there is such substance abuse multifinality, then it may be the case that significant variations in etiological factors relate to divergent subtypes of substance abuse. However, even if substance abuse is an instance of multifinality, this would not necessarily mean that substance abuse does not have a single underlying process. Such multifinality, if it exists, might result from the interaction of a single underlying process with a diverse range of external factors (e.g. the particular drugs which the individual uses or the protective social influences of the user's family) as well as a wide range of intrinsic factors (e.g. the individual's developmental level or co-occurring psychopathology). In any case, investigating the heterogeneity of etiological factors to identify differing patterns may lead to the identification of substance abuse subtypes and to the explication of their underlying processes. We examined the available research on risk factors for drug abuse to explore this possibility.

Our analysis of current research identified three emergent clusters of risk factors for substance use disorders: behavior disinhibition, affect dysregulation,

and conduct disorder/antisocial personality disorder (CD/ASPD) which will be referred to here as antisociality. Converging lines of research have found antisociality to be the most clearly established risk factor(s) for substance use disorders and as such, it will be the focus of this brief review.

3.1. Antisociality

Research shows that antisociality co-occurs with drug abuse, that antisociality confers substantial risk for the various stages of drug involvement ranging from initial drug use to drug dependence, that personality characteristics akin to antisociality are associated with drug abuse, and that the familial diathesis of drug abuse likely involves antisocial behavior and/or personality characteristics that may underlie the behavior.

Research on drug use disorders provides consistent and overwhelming evidence of substantial comorbidity between substance use disorders and antisocial personality disorder (ASPD), characterized by a pattern of irresponsible, impulsive and remorseless behaviors beginning in childhood or early adolescence and continuing into adulthood (APA, 1994). Findings from three large epidemiologic surveys, the Epidemiologic Catchment Area (ECA) survey, the NCS, and the International Consortium in Psychiatric Epidemiology (ICPE) show substantial comorbidity of ASPD with drug abuse and drug dependence (Kessler et al., 2001; Regier et al., 1990; Warner et al., 1995). Indeed, evidence from the ECA survey (Regier et al., 1990) shows that ASPD was the psychiatric disorder with the largest odds-ratio for both alcohol disorders (O.R. = 21.0) and drug disorders (O.R. = 13.4). Most recently, Grant and colleagues have shown that ASPD has markedly strong associations with alcohol and drug abuse and dependence in the general population (Grant et al., 2004). Moreover, the magnitude of comorbidity between antisocial personality disorder and drug involvement has been found to generally increase from drug use to drug dependence (Kessler et al., 1996; Merikangas et al., 1998; Swendsen and Merikangas, 2000). In the NCS, for example, the lifetime risk of adult antisocial behavior was 2.8 for drug abuse and 13.6 for drug dependence (Kessler et al., 1996).

Several studies have shown that the risk attributed to behavior problems increases with the progression from drug use to drug dependence suggesting an etiological link between antisociality and addiction. Robins and McEvoy (1990) reported that the likelihood of substance abuse increases with each conduct problem—a dose-dependent relation that helps support the argument that conduct is a cause of substance abuse problems. Several studies indicate that child psychopathology predicts heavier drug use in adolescence. Focusing on trajectories of drug use from ages 13-18 years, White et al. (2001) found that higher levels of attention-deficit/hyperactivity disorder and conduct disorder predicted higher levels of marijuana use. Lewinsohn et al. (2000) reported that persistent/frequent

smoking during adolescence was explained in part by comorbid behavior disorders. Former or current daily smokers, compared to smokers who never smoked on a daily basis, were nearly 4-times as likely to have conduct or oppositional defiant disorder (O.R. = 3.9).

Conduct disorder, the precursor of ASPD that manifests prior to age 16, has also been consistently reported as a risk factor for drug use. In a comprehensive review of fifteen community studies on adolescent substance use and abuse, Armstrong and Costello (2002) reported that behavior disorders were the psychiatric conditions that were most commonly associated with substance abuse. They estimated that substance users or abusers, compared to controls, were four times more likely to have conduct disorder, oppositional defiant disorder, or attention-deficit hyperactivity disorder. Focusing specifically on conduct disorder, several studies have found that this behavior problem is associated with particularly high risk of substance abuse (Armstrong and Costello, 2002; Chilcoat and Bresleau, 1998). The estimates are often higher among clinic samples. Burke, Loeber, and Lahey (2001) reported that conduct disorder was associated with a 6-fold increased risk of tobacco use in a sample of clinic-referred boys.

Aside from the full-blown diagnosis of conduct disorder, several prospective longitudinal investigations reveal childhood externalizing problems as a principal pathway in the development of substance use and substance use disorders (McCord 1981; Robins and McEvoy, 1990). Evidence from community samples includes a follow-up of the Baltimore site of the Epidemiologic Catchment Area survey that indicates that problem behaviors (e.g., fighting, school suspension, frequent lying) prior to the age of 15 was associated with increased risk of injection drug use at approximately 26 years of age (Neumark and Anthony, 1997). Lewinsohn et al. (1995) reported that externalizing behavior problems predicted substance use disorder over a one-year period during adolescence; Reinherz and colleagues (2000) found that hostile/aggressive behavior at age 9 predicted substance use disorder by age 21; and Storr et al. (2004) found that higher levels of teacher-rated childhood misbehavior at entry into primary school were associated with an increased risk of becoming tobacco-dependent by young adulthood. Such findings have helped construct an empirical basis for randomized field trials designed to test hypothesized mechanisms of association. In fact, there is evidence from a randomized study designed to decrease conduct problems that supports an etiologic link between conduct problems and subsequent substance use. Kellam and Anthony (1998) found that boys who were assigned to a 2-year behavior-improving classroom program, compared to boys assigned to usual classroom environments, were less likely to begin smoking cigarettes in early adolescence. In short, converging lines of evidence indicate that substance abuse and antisocial behavior are intimately connected problems of significant concern to public health.

It is likely that antisociality will be important in interpreting the well-established finding that a positive family history of substance abuse confers

substantial risk for substance use outcomes. Although controlled family studies demonstrate that drug disorders run in families (Bierut et al., 1998; Merikangas et al., 1998) and twin and adoption studies (Pickens et al., 1991; Grove et al., 1990; Jang et al., 1995; Tsuang et al., 1998; Kendler et al., 1999; Kendler et al., 2000) show that the familial clustering of drug abuse can be explained in part by genetic factors, the specific processes through which familial drug abuse exerts an influence is not clear. Evidence suggests that greater research attention to psychiatric comorbidity, particularly comorbid antisociality, may inform our understanding of such processes. Cadoret's classic adoption studies have suggested, for example, that the role of genetic factors in the development of drug abuse involves two paths from parent to adopted-away offspring. The first path indicates a direct association between substance abuse in the biologic parent and drug abuse in the adoptee. The second path indicates an association from antisocial personality disorder in the biologic parent to aggressive behavior in the adoptee, which in turn is associated with drug abuse in the adoptee (Cadoret, 1992; Cadoret et al., 1986; Cadoret et al., 1996).

There is some support for the notion that antisociality operates as a moderator for family history of drug abuse. Relying on follow-up data from Cadoret's sample, Langbehn and colleagues (2003) applied survival analyses methodology to age-of-onset data for both drug use and drug disorders in an attempt to examine whether family history of drug abuse with antisocial personality disorder poses greater risk than family history of drug abuse without antisocial personality disorder. When predicting both drug use and drug disorders in adoptees as young adults, results showed that the presence of drug abuse combined with antisocial personality disorder in the adoptee's biological father increases the risk for the development of drug problems in the adoptee. Similar findings have been reported in other samples. Moss and colleagues (2002) showed that adolescent offspring of fathers with substance dependence (with or without antisocial personality disorder) fared worse than those without substance dependence on several measures of family functioning. Yet, children of fathers with both substance dependence and antisocial personality disorder demonstrated the highest levels of externalizing and internalizing psychopathology as well as greater affiliation with deviant peers which, in turn, was associated with psychopathology. Chassin and colleagues (2002) found that adolescent offspring of alcoholics with comorbid antisocial personality disorder, compared to offspring of alcoholics only, were more likely to be classified into the high-risk group characterized by early and heavy drinking patterns.

4. CONCLUSIONS

In addition to the research on the association between substance use disorders and antisociality, there is a large body of literature reporting connections with

behavior disinhibition and affect dysregulation. It is not possible in this short chapter to review these and other findings on risk factors for substance use disorders. However, the above discussion illustrates the convergences in the research findings on risk factors that point to possible clusters having implications for further understanding the heterogeneity of substance abuse and the identification of drug abuse subtypes.

It is also not possible in this chapter to discuss important related issues, such as the relationship of heterogeneity to substance use disorder phenotypes and endophenotypes, the role of protective factors in the divergence of subtypes, the relationship of co-morbid psychiatric conditions and developmental psychopathology to heterogeneity, developmental influences, and individual and group diversity, and the implications of heterogeneity and subtypes for prevention and treatment. Despite the unanswered questions, however, it is clear that investigation of the heterogeneity of substance use disorders and their underlying processes can advance our ability to effectively understand, prevent and treat substance abuse.

It is clearly important to go beyond the recognition of the heterogeneity of drug abuse and to look for systematic variations in the etiology and manifest patterns of substance abuse. There may be critical variations in the underlying processes of substance abuse as well as significant systematic differences in the observable behavior patterns. Distinguishing major divergences in the differing patterns may lead to the identification of clinically significant subtypes, help determine the underlying processes of substance abuse, and facilitate the study of the ways in which environmental factors interact with individuals' characteristics (and the underlying processes of substance abuse) to result in different subtypes. While the available research does not answer the question of whether there are drug abuse subtypes, it does provide encouragement to continue the search.

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