Familial Factors and Substance Abuse: Implications for Prevention

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Several decades of research have revealed that the etiology of drug abuse comprises a complex network of interactive social, biologic, and genetic factors, which exhibits different levels of salience across development. There are several excellent summaries of the extensive literature on risk factors for drug use (Brook et al. 1990; Clayton 1992; Dembo et al. 1985; Hawkins et al. 1992; Kumpfer 1989; Swaim 1991), but far less is known about the risk and protective factors for drug abuse or dependence. Risk factors for drug abuse generally fall into three major domains: the individual, the family, and the social environment, which includes peer, school, neighborhood, and the broader cultural background. This chapter focuses on the role of familial factors in the etiology of substance abuse.

CURRENT KNOWLEDGE ON THE ROLE OF FAMILIAL FACTORS IN THE ETIOLOGY OF DRUG ABUSE

Family Studies

The familial aggregation of alcoholism and drug abuse has been well established. (For comprehensive reviews of alcoholism see Merikangas 1990 and McGue 1994; for drug abuse see Croughan 1985; Gordon 1994; and Rounsaville et al. 1991). Controlled family studies of alcoholic probands reveal a threefold increased risk of alcoholism and a twofold increased risk of drug abuse among the relatives of probands with alcoholism compared with those of controls. Numerous family history studies and systematic family studies of substance abusers in treatment settings (Croughan 1985; Gfroerer et al. 1988; Hill et al. 1977; Meller et al. 1988; Mirin et al. 1988, 1991; Rounsaville et al. 1991) reveal a significantly increased risk of both alcoholism and drug abuse among relatives when compared with population expectations. However, these findings are suggestive at best because of insufficient evidence from family studies, which employ contemporary family study methodology to investigate the familial patterns of drug abuse. The optimal methodology includes an epidemiological sample of pure and comorbid probands recruited from both treatment and community settings, direct interviewing of

available first-degree relatives, and a contemporaneous control group selected with similar methods.

To date, there are only two family studies of drug abusers in which relatives were interviewed directly (Mirin et al. 1991; Rounsaville et al. 1991) and only one family study with a non-drug-abusing control group (Rounsaville et al. 1991). Though the latter study was by far the most rigorous to date, the integration of controls from a separate family study limited the comparability of the groups of relatives because of differences in methodology.

In order to more accurately assess the risk of drug abuse in relatives, it is important to examine different generations or cohorts to take into account the availability of illicit substances across time periods. Family studies that investigated generational differences in the transmission of substance abuse revealed that drug use (Gfroerer 1987) and abuse (Merikangas et al. 1992) is elevated among siblings of drug abusers and that there is a direct relationship between parental drug use (Gfroerer 1987) and abuse (Luthar et al. 1992; Merikangas et al. 1992) and use and abuse in offspring. Furthermore, Merikangas and colleagues (1992) showed that there is a strong association between rates of drug abuse in siblings of opioid abusers and the number of parents with substance abuse.

High-Risk Studies

In recent years there has been a burgeoning empirical interest in children presumed to be at high risk for future psychopathology. Unfortunately, the high-risk study paradigm has been applied nearly exclusively to the major psychiatric disorders and to alcoholism. There is sparse information on the development of drug use disorders among young offspring of parents with drug abuse.

PATHWAY TO SUBSTANCE DISORDERS

The investigation of the risk of drug disorders in younger offspring of substance abusers is inherently limited by the fact that they have not yet passed through the period of risk for the onset of these disorders. However, psychopathology may be an intermediate outcome on the pathway to substance use disorders, which may be feasibly examined in this young group. For example, substance abuse has been found to be associated with the major psychiatric disorders—particularly anxiety and affective disorders—both in clinical samples and in the general

population (Anthony and Helzer 1991; Bukstein et al. 1989; Deykin et al. 1987). It is believed that persons with major psychiatric disorders may actually have an increased vulnerability to substance abuse, because the substance may ameliorate the symptoms of the underlying psychiatric condition (e.g., self-medication hypothesis).

A cross-sectional study of high school students found that children above the 85th percentile in anxiety were four times more likely to have used alcohol than those below this percentile (Walter et al. 1991). Moreover, Knop and colleagues (1993) recently demonstrated a specific association between anxiety in childhood and the subsequent development of alcoholism in a 30-year prospective longitudinal study of a large birth cohort in Copenhagen, Denmark. The evidence also suggests that deviant behaviors, conduct problems, and antisocial personality are strongly associated with both alcohol and illicit drug use/abuse (Kandel 1980; Robins and McEvoy 1990). A prospective study of a cohort of
8- to 12-year-olds by Boyle and colleagues (1993) showed that teacher-rated conduct disorder predicted the use of alcohol and hard drugs 4 years later. Although attention deficit hyperactivity disorder have been considered to be etiologically related to substance abuse, more recent evidence has suggested that the majority of hyperactive children who later abused drugs had conduct and/or oppositional defiant disorder either before or coincident with the onset of substance abuse.

The results of a community study by Rubio-Stipec and associates (1991), which linked parental and child disorders, showed an increased risk of internalizing rather than externalizing problems among the offspring of alcoholic parents. Likewise, Reich and colleagues (1993) found increased rates of overanxious disorder among offspring of alcoholic parents. One of the few high-risk studies of drug abuse has been described in a series of papers that report the results of a study of preadolescent sons of fathers with and without substance abuse who participated in a longitudinal study at the Center for Education and Drug Abuse Research (CEDAR) at the University of Pittsburgh (Moss et al. 1994). Although examination of the magnitude of substance abuse is precluded by the youthful age of this sample, several reports have presented information on behavior problems and temperamental factors associated with paternal substance abuse. An elevation in problem behaviors, namely externalizing conduct problems and socialization problems (Moss et al. 1994), increased rates of anxiety disorders (Moss et al. 1995) and higher levels of aggressivity, inattention, and impulsivity (Martin et al. 1994) than sons of non-substance-abusing fathers. Similarly, Gabel and Shindledecker (1992)

reported that sons of substance-abusing parents had more conduct diagnoses in association with severe aggressive/destructive behavior than sons of non-substance-abusing parents, while daughters of substance-abusing parents were more likely to receive attention deficit hyperactivity disorder and conduct diagnoses than the girls of non-substance-abusing parents. Wilens and colleagues (1995) likewise reported significantly elevated scores on dimensional symptom rating scales among the children of opioid-dependent parents.

SUBSTANCE DISORDERS

There are several studies that have investigated the link between parental and adolescent drug use (Duncan et al. 1995). Numerous studies of college students have examined the association between parent and offspring substance problems (Annis 1974; Fawzy et al. 1983; Meller et al. 1988; Scherer 1973; Scherer and Mukherjee 1971; Smart and Fejer 1972). Nearly all studies reported an association between alcohol and illicit drug use in parents and their college-age offspring. However, all of the latter studies employed self-report questionnaires regarding drug use in both parents and the students, thereby limiting the conclusiveness of the findings. In addition, a sample that has entered college may not be representative of all persons with a family history of drug use/abuse. Findings from a family history study of alcoholism revealed that the emergence of differences in risk of alcohol and other drug use among individuals with a parental history of alcoholism and controls may occur at the time of transition from late adolescence to early adulthood, which may be a critical period for the expression of substance use vulnerability (Pandina and Johnson 1989). Thus, studies that investigate early patterns of substance use and abuse among individuals at high and low risk for substance abuse may fail to discriminate between those with true vulnerability for substance use problems.

There are few studies of high-risk substance abusers with long periods of prospective observation of cohorts at high and low risk for the development of substance abuse. Individuals examined in the critical period from late adolescence to early adulthood must be followed prospectively to differentiate extended substance abuse from the heavy experimentation often seen in this period. One of the few studies involved a longitudinal Danish birth cohort at high and low risk for alcoholism based on a paternal history of alcoholism, which revealed that there was little difference in the drinking behavior of young men at age 20 (Schulsinger et al. 1986); however, at the

followup at age 30, substance dependence, but not abuse, was significantly more frequent among the male offspring of alcoholic fathers than among the male offspring of nonalcoholic fathers (Knop et al. 1993). These findings support the need for adequate followup intervals of high-risk youth to ensure that the majority of the cohort have passed through the age of risk for substance disorders and to clearly define the increase in substance-related problems that occur at different stages of development. In studies of high-risk cohorts, oftentimes little attention was paid to the mating type of the parents, as alcoholic fathers have been the primary exposure variable.

Among studies of high-risk young offspring of parents with alcoholism, findings have generally supported an increase in risk for the development of alcohol use, other drug use, and related problems (West and Prinz 1987). For example, Chassin and colleagues (1991) found parental alcoholism to be a significant risk factor for child symptomatology and substance use among 10- to 15-year-old offspring, with the risk found to be stronger among those offspring of parents with current rather than remitted alcoholism. Similarly, Johnson and associates (1989), Reich and colleagues (1993), and Hill and Hruska (1992) reported an increased risk of substance-related problems among the offspring of alcoholic parents. In a sample of college freshmen, Sher and associates (1991) found that children of alcoholics reported more psychiatric stress as well as more alcohol and other drug problems and received more diagnoses of alcohol disorders than the comparison group of subjects without a family history of alcohol and other drug disorders.

However, to date, there are no controlled studies of offspring of substance abusers other than alcoholics from which estimates of the risk of the development of drug abuse can be derived. As described below, the first wave of data from the Yale Family Study of Comorbidity of Substance Abuse and Anxiety Disorders provides the initial data on the risk of substance abuse and psychopathology among offspring of parents with alcohol or other drug abuse.

SPECIFIC FAMILY FACTORS

Genetic Factors: Twin Studies

There are an increasing number of twin studies that have provided evidence that genetic factors play a major role in the familial aggregation of substance use and abuse. Although most twin studies of substance abuse have focused on alcoholism, there are two published studies that have investigated twin concordance for other drug abuse or dependence in a large series of twins (Jang et al. 1995; Pickens et al. 1991). Pickens and colleagues (1991) found that both male and female monozygotic twin pairs had a 1_-fold increased risk of drug abuse compared with dizygotic pairs, but the heritability of drug abuse was significant only for males, possibly due to the low number of female pairs with substance abuse. Sex differences in the components of the genetic and environmental factors also emerged; the concordance for males could be attributed to both shared genes and environmental factors, whereas for females, the majority of variance was attributable to the unique environmental experiences of individual twins.

There are also several twin studies of use of specific drugs, including nicotine, caffeine, tranquilizers, and sedatives (Claridge et al. 1978; Gurling et al. 1985; Jang et al. 1995; Pedersen 1981), and components thereof. The highest twin correlations were reported for nicotine (0.84) and caffeine (0.78) in Pedersen's (1981) study of the Swedish twin registry. Jang and associates (1995) reported a moderate degree of heritability for the frequency of use and the tendency to use of numerous illicit substances ($h^2 = 0.32$).

The results of a large-scale twin study of male Vietnam era veterans have recently become available (Tsuang et al. 1993). The major results suggest that (1) substance abuse is highly heritable, (2) the contribution of genetic factors is more significant for frequent use or abuse than for nonproblematic use, and (3) the influence of genetic factors, shared environment, and the unique environment each contributes to the development of substance abuse. Additional analyses of data from this twin registry reveal that some of the subjective effects of marijuana, including suspiciousness and agitation, are under genetic control (Tsuang et al., in press).

One of the strongest sources of evidence regarding the role of genetic factors in the etiology of drug abuse derives from monozygotic twins reared apart. Grove and colleagues (1990) examined the concordance

for alcoholism, drug abuse, and antisocial personality disorder among monozygotic twin pairs separated at birth. The heritability estimate of drug abuse of 0.45 far exceeded that of alcoholism of 0.11. Furthermore, drug abuse was strongly associated with conduct disorder in childhood and antisocial personality in adulthood. These findings suggest that genetic factors explain a large proportion of the variance in the development of drug abuse and that a large proportion of the heritability of substance abuse in adulthood can be attributed to shared genetic factors that underlie the development of behavior problems in childhood (Grove et al. 1990).

EVIDENCE FOR SPECIFIC VULNERABILITY GENES: BIOCHEMICAL/GENETIC MARKERS

Studies of associations between genetic markers or their biologic products have yielded no consistent biologic markers for drug abuse. The lack of findings is not unexpected in light of the heterogeneity of substance abuse, differential patterns of comorbidity with disorders that are also under some degree of genetic control, and the very nature of drug abuse resulting from gene-environment interaction at the level of exposure as well as subsequent use and abuse.

Of particular importance are the specific neurochemical mechanisms through which the genetic factors described above exert their influence. Aside from the investigation of alcohol metabolism, there has been little research on metabolism as well as the affective and cognitive effects of specific drugs in high-risk samples for obvious ethical reasons. However, etiologic models of the development of drug abuse need to include the role of the specific effects of various drugs in either enhancing or reducing subsequent exposure to drugs. More information could be accumulated indirectly in observational studies by systematically inquiring about specific effects of drugs and drug(s) of preference.

SPECIFIC GENETIC AND ENVIRONMENTAL FACTORS: ADOPTION STUDIES

The optimal study paradigm for discriminating the role of genetic and environmental factors and their interaction in the development of a disorder is the cross-fostering study in which either (1) adoptees with biologic vulnerability are reared in homes of non-drug-abusing

adoptive parents or (2) adoptees who lack a parental history of substance abuse are reared in homes of parents with substance abuse. Such studies can determine the effects of biologic vulnerability and environmental exposure to substance abuse and their mutual influence in the risk of substance abuse. The classic adoption studies of Cadoret and colleagues (1986, 1992, 1996) have been highly informative in elucidating the role of genetic factors in the development of drug use and abuse in a U.S. sample. The major results of their studies reveal that genetic factors play a far more important role in the transition from drug use to abuse than in drug use itself. Additionally, their work identifies two major biologic/ genetic pathways to the development of drug abuse in adoptees: One that is driven by substance abuse in the biologic parent and is limited to drug abuse and dependence in the adoptee and another that appears to be an expression of underlying aggressivity and is related to criminality in the biologic parent (Cadoret et al. 1995). These pathways to drug abuse were recently confirmed in a study of female adoptees by the same group of investigators (Cadoret et al. 1996). Exposure to a sibling or peer with deviant behavior appears to contribute to the development of drug use but not abuse. None of the adoption studies have thus far been able to detect a gene-environment interaction in the genesis of drug initiation or in the transition from use to abuse (Cadoret 1992).

Summary

In summary, the results of family, twin, and adoption studies of substance abuse reveal that both drug use and abuse are familial and that genetic factors explain a substantial proportion of the variance in the etiology of drug abuse. Factors associated with increased familial aggregation of drug abuse include male gender, parental concordance for drug abuse, and comorbid psychopathology, particularly alcoholism and antisocial behavior. Drug dependence is far more heritable than either drug use or abuse, and genetic factors appear to be more important in the transmission of drug problems among males. The results regarding the role of genetic factors in the persistence, but not initiation, of certain substances confirm findings in animals (Marley et al. 1991). These findings are particularly interesting when all three sources of genetic evidence also suggest two independent pathways to drug abuse; one in which shared etiologic factors influence the development of antisocial personality and drug use and another that appears to underlie the development of drug dependence. However, there is a striking lack of controlled family studies of substance abuse. These studies are critical for elucidating the role of genetic and environmental factors in the transmission of

substance abuse, validating phenotypic definitions of substance use/abuse, and identifying sources of heterogeneity in the etiology of substance abuse, particularly with respect to the role of comorbid psychiatric disorders and polysubstance abuse.

MECHANISMS FOR FAMILIAL TRANSMISSION

Family Factors Specific to Drug Abuse

There are several specific and nonspecific environmental mechanisms through which parents may convey increased risk of substance abuse to their offspring. The mechanisms through which families may enhance the risk of drug use and abuse in their offspring include the following:

- Specific factors
  - Exposure to drugs
    - Modeling of drug use
    - Parental concordance for drug abuse

- Nonspecific factors
  - Disrupted family structure
    - Marital discord
    - Impaired parenting
    - Exposure to stress
    - Family psychopathology
    - Neglect
    - Abuse

Aside from transmission of genetic factors that determine the physiological effects of drugs and metabolism, the family may also enhance the risk of drug abuse through several factors specific to drug use as well as a broad range of nonspecific factors that characterize homes of parents with dysfunction secondary to a psychiatric or somatic illness. Parents may directly influence the use and abuse of drugs in their offspring through (1) exposure to drugs in the prenatal phase of development, (2) providing negative role models in terms of general use/abuse of drugs or the use of drugs as a coping mechanism, or (3) enhancing the availability of drugs.

Several investigators have examined the role of exposure to parental drug use and the risk of drug use among offspring of parents with substance abuse (Duncan et al. 1995). The use of other drugs or alcohol as a coping strategy among parents may serve as a model for the development of maladaptive coping skills among

offspring (Patterson 1986). Several studies have found that in addition to exposure to parental drug use, parental attitudes toward drug use may also play a key role in the attitudes and behavior related to drug use among offspring (Barnes and Welte 1986; Brook et al. 1986). The effects of either direct modeling of parental substance use or the tendency to use substances as a coping mechanism have been shown to have far smaller effects on drug use in offspring than other parent influences, chiefly those involving the quality of the parent-child relationship and parental monitoring of the behavior of their adolescent offspring (Molina et al. 1994).

Nonspecific Family Factors

As listed in table 1, nonspecific factors through which parental drug abuse and its sequelae may influence offspring include disrupted family structure, exposure to marital discord, impairment in parenting behavior, exposure to high levels of both acute and chronic stress, social deprivation, and physical, sexual, and emotional abuse. The high divorce rates among substance abusers may also be associated with an elevated risk of the development of substance abuse in offspring and deviant behavior in general due to the nonintact home and disrupted family structure. Such families have been found to have less stability and more moves and thus require coping and adaptation strategies that may far exceed the ability of exposed youngsters (Peterson and Zill 1986; Zimmermann-Tansella et al. 1988). Clair and Genest (1987) reported that the families of alcoholic children were far more dysfunctional than those of controls. Furthermore, Smart and Chibucos (1990) found that adolescents who came from extreme families were especially vulnerable to substance use. Social stress emanating from the disruptive family environment of substance-abusing parents has also been shown to increase drug use among exposed adolescents (Rhodes and Jason 1990).

The parental marital relationship does not appear to have a direct impact on drug use, although it does appear to interact with other risk factors in enhancing the risk of drug use (Kaplan 1995). However, some investigators have noted that family conflict is associated with the youngster's delinquency and drug use (Robins 1980). Indeed, parental conflict may be a greater risk factor than disrupted family structure resulting in parental absence (Farrington et al. 1988). Adolescents with substance-abusing parents experience more stress (Brown 1989) and more negative life events than those from non-substance-abusing families (Roosa et al. 1990).

Parental substance abuse may also contribute to family dysfunction, which is then related to such negative outcomes as the initiation or escalation of substance abuse (Gabel and Schindledecker 1991; McCarthy and Anglin 1990). Dysfunction in the relationships between parents and adolescents is also associated with an elevated risk of adolescent substance abuse. Substance-abusing parents have been shown to provide less social or emotional support to their children (Holden et al.

1988). Evidence from several studies reveals that strong parent-child bonding may inhibit drug use and delinquent behavior in adolescents (Hawkins et al. 1992), whereas poor relationships are associated with an increased risk of drug use in offspring (Brook et al. 1980, 1986). Whereas poor communication and lack of parental support may directly lead to adolescent substance use, Brook and colleagues (1990, 1993) showed that drug use by an adolescent offspring may serve to further disturb parent-child interaction (Brook et al. 1990, 1993; Kaplan 1995; Kumpfer and Hopkins 1993).

The effect of maternal drug use on parenting and the subsequent use of drugs in offspring was described by Kandel (1990), who found a strong relationship between maternal drug and control problems with their children. Subsequent studies have shown that poor parental control is associated with drug use. Molina and associates (1994) found that both parental monitoring and socialization were associated with substance use, irrespective of whether the parent was alcoholic. In contrast, increased levels of parental monitoring or control (Baumrind and Moselle 1985; Duncan et al. 1995) were associated with a decreased risk of substance use in offspring. Likewise, Brook and colleagues (1986, 1988) found that both parental control and attachment served to inhibit drug use among adolescents. Appropriate parental monitoring was also effective in reducing delinquency (Patterson et al. 1982). These studies all provide support for the current notion that the family is the single most influential childhood factor in buffering the child and in shaping later adaptation (Kumpfer 1987).

The relationship between parental substance abuse and childhood behavioral problems indicative of abuse or maltreatment was studied by Gabel and Shindledecker (1990) in a sample of children hospitalized for suicidal ideation/behavior or aggressive/destructive behavior. The results revealed that parental substance abuse and suspected maltreatment were the major indicators of confirmed cases of child abuse. Even more commonly associated with parental substance abuse is neglect, which can have major physical and emotional consequences for exposed children.

ILLUSTRATIVE EXAMPLES FROM THE YALE FAMILY STUDY OF SUBSTANCE ABUSE

The next section describes the results of a large-scale family study of substance abuse, which provides preliminary evidence to support the role of familial factors in the development of substance abuse. The major goals of the study were to investigate the magnitude and patterns of transmission of substance abuse in families and the role of parental other drug and alcohol abuse on the development of emotional and behavioral problems and substance use and abuse among offspring.

Sample Characteristics

A total of 299 probands were selected from outpatient specialty clinics for substance abuse (drug abuse/dependence and/or alcohol abuse/dependence) disorders at the Connecticut Mental Health Center (New Haven, Connecticut) or through a random digit dialing procedure in the greater New Haven area. The probands were assigned to one of five lifetime diagnostic groupings based on an algorithm designed to reflect predominant levels of psychopathology. The groupings were as follows: 27 probands with cocaine abuse/dependence, 87 probands with opioid abuse/dependence, 35 probands with a *Diagnostic and Statistic Manual of Mental Disorders (Third Edition, Revised) (DSM-III-R)* diagnosis (American Psychiatric Association 1987) of drug abuse of the anxiolytic class (e.g., marijuana, sedatives, benzodiazepines), 89 probands with a *DSM-III-R* diagnosis of alcohol abuse/dependence, and 61 normal controls with no history of a *DSM-III-R* Axis I disorder. Assignment to a substance cell was based on an algorithm that incorporated the subjective report of the substance of choice and predominant substance of abuse/dependence based on quantity, frequency, and chronicity. All probands were directly interviewed according to the procedures described below. Probands were excluded from the study if there was evidence of significant organic mental impairment or if they were found to have schizoaffective disorder or schizophrenia.

Interview Procedures

Once consent for participation in the study was obtained from the probands, they were directly interviewed, and a pedigree was generated that identified spouses, ex-spouses with whom probands had children, and all first-degree biological relatives. The proband provided family history data on all first-degree relatives. The interviewer was kept blind to the diagnostic grouping of the proband. Permission to contact first-degree relatives as well as their addresses and phone numbers was obtained at the initial interview. An independent interviewer, blind to the diagnosis of the proband, was then assigned to contact the spouse or first-degree relatives of the proband. Children of the proband younger than age 18 were enrolled in a high-risk study using parallel as well as additional measures. Relatives were directly interviewed either by telephone or in person.

The total sample included 280 probands who had 1,267 first-degree adult relatives. Approximately equal proportions of relatives were interviewed when compared across proband groupings.

Assessments

The diagnostic interview for adults was the semi-structured Schedule for Affective Disorders and Schizophrenia (SADS), current and lifetime versions (Endicott and Spitzer 1978), extensively modified to obtain *DSM-III* and *DSM-III-R* criteria (American Psychiatric Association 1987). The major modifications of this instrument included (1) addition of an open-ended section designed to facilitate rapport between the interviewer and subject as well as target key diagnostic sections to be completed, (2) addition of questions on the interrelationships of disorders in terms of temporal sequence and shared symptomatology, (3) elicitation of information on psychiatric disorders and subthreshold manifestations of the key criteria for multiple diagnostic systems, (4) the application of a polydiagnostic approach through the assessment of the criteria for multiple diagnostic systems, and (5) the expansion of the substance abuse sections to obtain more detailed information on the patterns of use of each drug class and their interrelationship and on the course of alcohol and other drug use and abuse.

Family History Information

Family history information was obtained using a modified version of the Family History-Research Diagnostic Criteria (FH-RDC) developed by Andreasen and colleagues (1977) for data collected by the family history method that was modified to obtain both *DSM-III* and *DSM-III-R* diagnoses in adults and children and to obtain more detailed information on alcoholism and anxiety disorders for the purposes of this study. The interviewer first obtained a brief open-ended summary of the interpersonal characteristics and history of emotional or behavioral problems and then inquired about the quality and frequency of contact that the interviewee had with the target relative. Key probes regarding each major diagnostic category of *DSM-III-R* Axis I, as well as antisocial personality disorder, selected childhood disorders, and other behavioral problems were then discussed.

Interviewers

All interviewers had an adequate level of clinical training in clinical psychology, school psychology, or social work and underwent a series of formal training sessions with the training package in family study methods that the authors developed. All of the interviewers were required to demonstrate interrater reliability of ratings with ratings of the tapes and supervised coratings of live subjects. Each interview was reviewed by a psychiatrist or psychologist who provided ongoing supervision of the interview process.

Diagnostic Procedures

The clinical interviewers assigned diagnoses to each interview according to *DSM-III-R* criteria. A psychiatrist blind to the diagnosis of the proband then reviewed each case and provided feedback to the interviewers to resolve diagnostic ambiguities.

Procedures for the "best-estimate" diagnoses on interviewed subjects used by the authors' team were an expansion of Leckman and colleagues' (1982) original protocol. The final diagnoses were based on all available information, including the diagnostic interview, family history reports on each proband and relative, and medical records. All cases were subjected to initial review by clinical psychologists and doctoral students in psychiatric epidemiology. Reliability among reviewers was established by having the group follow general rules and guidelines highlighted in a procedures manual as well as corate a number of cases independently. Discrepancies between the initial diagnostic review and best-estimate diagnosis were resolved jointly by a team of clinicians.

Sample of High-Risk Children

The present study also involved an epidemiologic sample of high-risk children and adolescents of parent probands with alcoholism and/or substance abuse/dependence of the anxiolytic type or no psychopathology. Families in the high-risk component of the study included a total of 87 families of 52 probands diagnosed with anxiolytic, sedative, or benzodiazepine abuse, marijuana abuse or dependence, or alcoholism (substance group) and 35 proband controls having no history of psychiatric disorder (normal group). A total of 137 biological offspring ages 7 to 18 were eligible for interview in this study, of whom 134 (98 percent) were interviewed directly.

A modified version of the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E) was used for diagnostic assessment of the children (Chambers et al. 1985; Orvaschel et al. 1982). The K-SADS-E has been found to be a reliable and valid instrument for obtaining lifetime diagnoses on prepubertal children by its authors (Orvaschel et al. 1982) and on adolescents by others (Chambers et al. 1985; Gammon et al. 1983). Test-retest reliability following a short interval of time ranged from 0.41 to 0.81 (intraclass correlation coefficient) for summary scales. The reliability of diagnoses ranged from 0.24 to 0.70 (kappa statistic).

In the present study, the K-SADS-E was administered by a clinical psychologist blind to the diagnosis of the parent. The interview was administered independently with the child and with the mother about the child by the same interviewer. A best-estimate procedure for diagnoses was applied to the children in the present study (Leckman et al. 1982). This diagnosis is based on all available information, including the diagnostic interview, family history reports on the child, teachers' reports, and medical records. The diagnosis was made by a psychiatrist who was blind to the diagnostic status of the parents and who was not involved in direct interviews. If the subject met criteria for any psychiatric disorder, the records were reviewed independently by a second diagnostician.

Parent-Child Relationship

The Yale Family Study used the Parental Bonding Instrument (PBI) (Parker et al. 1979), which is a self-report measure of two dimensions of parenting—care and protection. These dimensions have been investigated individually and jointly (quadrants) with respect to offspring psychopathology. Twenty-five attitudinal and behavioral items were completed on both parents by each offspring. In addition, the parent who was directly interviewed about the child also completed a PBI describing their parenting behavior toward that specific child. The PBI has high test-retest reliability (Mackinnon et al. 1989; Plantes et al. 1988; Warner and Atkinson 1988).

Family Functioning

The Family Adaptability and Cohesion Evaluation Scale (FACES) was used to assess family functioning. The FACES III is a 111-item self-report instrument that measures family cohesion and adaptability and includes a social desirability scale (Olson et al. 1985). The overall FACES has demonstrated acceptable internal consistency (0.62 to 0.77) and test-retest reliability (0.80 to 0.83) as well as content and construct validity. With respect to the self-report version of the FACES used in this study, it has recently been demonstrated that the scores should be interpreted linearly (Olson 1991). Each interviewed family member (older than age 11) assessed his or her perception of the family's cohesion and adaptability by self-report.

In addition to the FACES-III, interviewed adults (older than age 18) also completed the McMaster Family Assessment Device (FAD) to measure family functioning (Epstein et al. 1983). The FAD is a 60-item self-report measure that contains seven subscales: (1) problemsolving, (2) communication, (3) family roles, (4) affective responsiveness, (5) affective involvement, (6) behavior control, and (7) general functioning (overall measure of family health/pathology). In addition to the use of continuous scores, subscale cutoffs have been established (Miller et al. 1986).

MAJOR FINDINGS

Familial Aggregation of Substance Abuse

Table 1 presents a summary of the results of analyses of familial transmission of alcoholism and other drug disorders in the adult relatives according to the presence of alcohol or other drug disorders in the proband. Each of these models controlled for relevant confounders of the relationship between proband and relative substance abuse, including sex of the proband and the interview status, age, and sex of the relative.

The results of table 1 reveal that after controlling for polysubstance abuse and other covariates in the proband and relative, alcoholism in the proband was associated with significantly elevated risk ratios of alcoholism in the relatives (OR = 4.1). This confirms the well-established familial aggregation of alcoholism in families. Other drug disorders in probands were associated with other drug disorders in relatives, with a risk ratio of 3.7. There was no increase in other drug disorders among relatives of alcoholic probands or vice versa. Indeed, other drug abuse/dependence in the proband was associated with a lower risk of alcoholism in relatives (OR = 0.5). These findings suggest some degree of specificity of transmission of alcoholism and other drug abuse/dependence in families.

Substance Abuse in Offspring

The rates of alcohol and other drug abuse among the adolescent offspring of these probands are presented in table 2. Although the mean age of the sample is only 12, a striking association emerges between parental substance dependence and alcohol and other drug abuse among the offspring. Whereas none of the offspring of parents without substance abuse or psychopathology exhibit substance abuse problems, 20 percent of the offspring of the substance-abusing parents meet criteria for alcohol or other drug abuse. Rates of alcohol abuse are twofold greater than those of other drug abuse, but no major sex differences emerged at this early stage of development. These findings suggest that the offspring of parents with other drug abuse are at increased risk for the development of substance abuse themselves. This is particularly striking when one considers the youthful age of this cohort and the inclusion of probands with either marijuana or anxiolytic abuse rather than “hard” drugs such as cocaine or opioids.

TABLE 1. *Substance abuse in relatives of probands with alcoholism and other drug abuse.*

Factors in Model	Disorders in Relatives	
	Alcohol N = 312	Other Drug N = 157
Proband		
Other drug	0.5 ($p < 0.01$) (0.4 - 0.7)	3.7 ($p < 0.01$) (2.3 - 5.9)
Alcohol	4.1 ($p < 0.01$) (2.8 - 6.0)	1.1 (0.7 - 1.9)
Sex	1.2 (0.9 - 1.7)	1.8 ($p < 0.05$) (1.2 - 2.8)
Relative		
Other drug	5.8 ($p < 0.01$) (3.9 - 8.8)	
Alcohol		6.0 ($p < 0.01$) (3.9 - 9.1)
Sex	0.4 ($p < 0.01$) (0.3 - 0.5)	0.6 ($p < 0.10$) (0.4 - 0.9)
Age	1.0 (0.99 - 1.01)	0.9 ($p < 0.01$) (0.92 - 0.95)
Interview Status	2.4 ($p < 0.01$) (1.7 - 3.4)	1.6+ (0.99 - 2.5)

TABLE 2. *Substance abuse in offspring older than age 12, by parental substance abuse.*

Disorders in Children	Parent Proband					
	Substance			Normal		
Sex of child	M	F	Total	M	F	Total
N of children > 12	N = 19	N = 20	N = 39	N = 14	N = 14	N = 28
Total alcohol/other drug abuse/dependence	21.1	20.0	20.5	0	0	0
Alcohol abuse/dependence	15.8	20.0	18.0	0	0	0
Other drug abuse/dependence	5.3	15.0	10.3	0	0	0

Family Environment of Substance Abusers

Families share their environment as well as their genes, and both biology and environment may increase their common risk for various psychiatric disorders. Physical (family structure and socioeconomic status) as well as social (family functioning including dyadic relationships) characteristics constitute the family environment. Parental psychopathology has been associated with increased rates of marital discord and both divorce and separation. However, the effects of parental psychiatric status appear global and impact negatively on parenting and overall family functioning.

The associations observed between parental psychopathology and parenting/family variables are important because of their potential impact on the mental health of offspring. Low levels of care from parents have been associated with offspring psychopathology. Marital distress as well as unhealthy family functioning styles were also associated with both mood and behavior disorders. Both extremes of the range of family cohesion and adaptability have been associated with offspring psychopathology.

Table 3 presents selected family structure and function domains for high- and low-risk families.

TABLE 3. *Family/home environment of children by proband parent group.*

Family Characteristics	Proband Parent		
	Substance (N = 77)	Normal (N = 54)	*p*
Parents divorced (%)	28.4	2.9	< 0.001
Low socioeconomic status (%)	40.3	20.0	< 0.01
Parent family functioning			
Parental care (mean score)	21.0	26.0	< 0.01
Family cohesion (mean score)	3.4	4.2	< 0.01

Offspring of substance abusers were less likely to be living with both parents and more likely to be in a group of lower socioeconomic status. With respect to the care dimension of parenting style, parents with substance disorders had significantly lower care scores. In addition, families with a substance-abusing parent had lower family cohesion scores. Family functioning was further examined by parental mating type. Those families with two affected parents had higher proportions of unhealthy functioning regardless of the particular combination of parental diagnoses. Although the rate of unhealthy functioning was elevated in the one-substance parent group, it did not significantly differ from the neither- affected mating type. The findings regarding family cohesion are similar, with those families with two affected parents (one of whom has a substance abuse diagnosis) being significantly more disengaged than comparison families.

Lower family cohesion was associated with both internalizing and externalizing diagnoses in the offspring. Female offspring showed an increase in internalizing disorders in families with poorer overall family functioning. Offspring of affected parents are subjected to multiple environmental risks for psychopathology.

IMPLICATIONS FOR PREVENTION AND TREATMENT

The results of this review suggest that a family history of substance abuse is one of the most potent risk factors for the development of substance abuse among exposed offspring. Both specific and nonspecific factors in the family contribute to the increased risk of drug abuse. The results of this study confirm the findings of the family history studies of Hill and colleagues (1977), which reported independent familial transmission of alcoholism and opioid abuse and that of Meller and associates (1988), which demonstrated the specificity of transmission of alcoholism and other drug abuse in relatives of probands with substance abuse. The moderate degree of independence of familial alcoholism and drug abuse suggests that the knowledge gleaned from the large body of research on family and high-risk studies of alcoholism may not apply to families of drug abusers. Moreover, the authors' family study data provide some evidence for specificity of transmission of the individual classes of drug abuse after controlling for the effects of antisocial personality among the probands. This suggests that there may be some vulnerability factors that predispose to the development of dependence on specific classes of drugs rather than to deviant behavior in general. Likewise, Gfroerer and colleagues (1988) and

Duncan and associates (1995) found a direct link between parental and offspring marijuana use that in the former study was not influenced by parental nicotine or alcohol use. Similar results emerged from studies of parent-child concordance for nicotine abuse (Bauman et al. 1990). These findings confirm the results of the longitudinal studies of children who yield two distinct general pathways to the development of drug abuse: one, which represents a manifestation of a generalized pattern of behavioral disturbances, including behavioral disorders in childhood, and another more heterogeneous pathway, which may result from a constellation of individual vulnerability factors for the development of dependence of specific classes of drugs. Emotional and behavioral disorders in childhood are a particularly key domain of vulnerability that require further recognition and evaluation.

This work suggests that future research should seek an understanding of the mechanisms through which the family conveys an increased risk of drug abuse to offspring, since a family history of substance abuse is the most potent predictor of vulnerability to its development. Study designs that incorporate the complexity of factors involved in familial transmission—including genetic factors, transmitted biologic factors, social and cultural factors, and nontransmitted biologic and social factors—are critical to gaining an understanding of these processes. The genetic epidemiologic approach is one of the most powerful in understanding the mechanisms through which families exert their influence on the transmission of drug abuse across generations to incorporate the components of the host vulnerability; factors associated with exposure to drugs; and the contribution of the family, peer neighborhood, and larger cultural environment conducive to its development.

Evidence presented in this chapter strongly supports the critical importance of family-based prevention programs for prevention of substance abuse. The findings suggest that targeted prevention should be geared toward offspring of substance abusers, even those who have not been identified in treatment settings. The majority of the substance abusers in the present study were identified from a random community sample, yet the magnitude of drug abuse in their offspring even at this early stage of adolescent development was quite striking.

These findings also have important implications for both primary and secondary prevention efforts. Primary prevention programs should seek to evaluate risk factors for the development of substance abuse, including both parental and family factors and individual characteristics of the children, which may be associated with elevation in the risk of drug abuse, particularly psychopathology such as

conduct problems and depression/anxiety. Comprehension of the complex interrelationships among individual, familial, and broader social environment is critical to reduce continued substance abuse in both adults and children. This suggests that a combination of individual and family treatment in conjunction with broader efforts toward education and prevention at the community level will provide the optimal approach to reduce substance abuse.

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