ORIGINAL ARTICLE

Co-occurrence of Abuse of Different Drugs in Men

The Role of Drug-Specific and Shared Vulnerabilities

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Background: Previous research has demonstrated genetic and environmental influences on abuse of individual substances, but there is less known about how these factors may influence the co-occurrence of abuse of different illicit drugs.

Methods: We studied 3372 male twin pairs from the Vietnam Era Twin Registry. They were interviewed using the *Diagnostic Interview Schedule, Version III, Revised* to investigate the extent to which the abuse of different categories of drugs occurs together within an individual, as well as the possibility that genetic and environmental factors are responsible for observed co-occurrence. Co-occurrence was quantified using odds ratios and conditional probabilities. Multivariate biometrical modeling analyses were used to assess genetic and environmental influences on co-occurrence.

Results: Abusing any category of drug was associated with a marked increase in the probability of abusing every other category of drugs. We found evidence for a shared or common vulnerability factor that underlies the abuse of marijuana, sedatives, stimulants, heroin or opiates, and psychedelics. This shared vulnerability is influenced by genetic, family environmental, and nonfamily environmental factors, but not every drug is influenced to the same extent by the shared vulnerability factor. Marijuana, more than other drugs, was influenced by family environmental factors. Each category of drug, except psychedelics, had genetic influences unique to itself (ie, not shared with other drug categories). Heroin had larger genetic influences unique to itself than did any other drug.

Conclusion: There are genetically and environmentally determined characteristics that comprise a shared or common vulnerability to abuse a range of illicit drugs.

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AN IMPORTANT issue in the investigation of vulnerability to drug abuse is whether there is a specific vulnerability for 1 drug (such as cocaine), a class of drugs (such as stimulants),[1-6] or psychoactive substances in general. Glantz[7] suggested that, at least for some abusers, the particular drug abused is almost incidental; it is the effect that motivates the individual. Abusers may use different drugs in different fashions to try to obtain the desired effect. In criticizing disease models of substance abuse because they imply that each type of addiction has a specific etiology, Tarter and Mezzich[8(p171)] concluded that "there is no definitive evidence indicating that individuals who habitually and preferentially use one substance are fundamentally different from those who use another." A generalized behavioral disposition, or risk, is supported by the following observations: (1) individuals who terminate abuse of one substance often initiate use of another; (2) no vulnerability factors have been identified that indicate risk for one particular substance; and (3) there is little evidence that abuse of any drug, such as marijuana, cocaine, heroin, or alcohol, "breeds true" within a particular family. Molecular, behavioral, and cellular research have elucidated central nervous system pathways that affect responses to ethanol, central nervous system stimulants, opiates, and marijuana[9-11] and suggest unique as well as shared mechanisms of sensitivity, neuroadaptation, and reward.

See also pages 964, 973, and 982

Considerable evidence[12-17] has been adduced to demonstrate genetic influences on substance abuse. Crabbe et al[18] reported the results of a multivariate analysis that characterized responses of 15 strains of mice to several doses of ethanol, pentobarbital, diazepam, and morphine. They found notable common patterns of genetic regulation of response to several variations of exposure to these drugs. Other animal studies[19-23] have shown that genetically mediated patterns of reinforcement from

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PARTICIPANTS AND METHODS

STUDY POPULATION

Participants were 6744 members of the Vietnam Era Twin (VET) Registry. The registry, assembled from Department of Defense computerized military records,[26] comprises male twin pairs born between 1939 and 1957 in which both members served in the military during the Vietnam War era (1965-1975). Zygosity was determined using a questionnaire and blood-group typing—a method that achieved 95% accuracy.[27] Of 10 300 eligible individuals (5150 pairs), 47 were deceased or incapacitated. Of the remaining men, 8169 (79.7%) were successfully interviewed by telephone. The 1874 monozygotic and 1498 dizygotic pairs in which both members responded to the drug abuse items are the subject of this report. Of all pairs recruited for the study, 66.1% were pairs in which both twins participated. The mean age of respondents was 44.6 years (SD, 2.8 years; range, 36.0-55.0 years); 90.4% were non-Hispanic white; 4.9%, African American; 2.7%, Hispanic; 1.3%, Native American or Alaskan Native; and 0.7%, "other." Precisely 33.3% were high school graduates and 38.6% were college graduates; 92.6% were employed full-time and 1.8% were employed part-time. Registry members live in all 50 states.

Subjects were interviewed using the *Diagnostic Interview Schedule, Version III, Revised*[28] (*DIS-III-R*). Interviews were performed by telephone by the Institute for Survey Research at Temple University (Philadelphia, Pa). Interviewers were trained by one of the investigators (M.J.L.) and their supervisor, who had attended a training course at Washington University, St Louis, Mo, conducted by the developers of the *DIS-III-R*. Telephone interviews were used instead of face-to-face interviews because of the geographical diversity of the sample. A number of studies[29-31] have supported the comparability of telephone and face-to-face interviews; these studies will be discussed later. The average length of the interviews was approximately 45 minutes.

The structured questions from the *DIS-III-R* that assess abuse and dependence symptoms according to *DSM-III-R*[32] were read to subjects who acknowledged using a drug more than 5 times. We use the term *drug abuse* to refer to substance abuse or substance dependence as defined by *DSM-III-R*.

DATA ANALYSIS

Using the following methods for quantifying the extent to which abuse of one drug is associated with abuse of a different drug, we assessed the relationship among the various categories of drugs within individuals. The first method is to calculate the conditional probability of the abuse of drug A, given that the individual is an abuser of drug B. The second method is to calculate the odds ratios, which give the odds of abusing drug A if the subject is an abuser of drug B, compared with the odds of abusing drug A if the subject is not an abuser of drug B. The third method uses the tetrachoric correlation, which is calculated from the 2×2 contingency table by assuming that the dichotomous outcome reflects an underlying normally distributed vulnerability with a threshold that divides abusers from nonabusers.

When phenotypes (eg, marijuana abuse) are correlated, as in the present study, multivariate models are fit to the traits jointly to assess the determinants of the observed phenotypic correlations. Multivariate structural equation modeling[33] permits assessment of whether genetic and environmental effects on a number of phenotypes correlate. The influence of additive genetic and family environmental effects are assessed by fitting a series of structural equation models to the data. In the first step, a full model is fit to the data that includes the effects of additive genes (A), family environment (C), and nonfamily environment (E) (E includes influences specific to an individual and random error). This model (ACE model) is compared with reduced models that delete either additive genes or family environment. Correlated genetic and environmental effects on each category of drug are tested statistically by comparing the fit of the full multivariate model to reduced models that delete subsets of effects. These estimates are determined using structural equation modeling implemented with LISREL[34] and weighted least squares.[33] The inverse of the asymptotic variances of the correlations are used as weights. A χ^2 difference test is used to determine if the null hypothesis (no decrement in the fit of the model) can be rejected. The best-fitting model is selected on the basis of parsimony (ie, the model with the fewest included parameters) from among the submodels that cannot be rejected at the .05 α level.

A number of models to characterize the mechanism or mechanisms underlying co-occurrence among the drug categories are fit to the data.

The single independent pathway model assumes that there is 1 genetic factor (A) that contributes to abuse of each category of drug and allows for the possibility of genetic influences that are unique to each individual category of drug. The model also assumes that there are a single family environmental factor (C) and a single nonfamily environmental factor (E) that contribute meaningfully to abuse of each category of drug and allows for family and nonfamily environmental influences that are specific to each drug. Co-occurrence across the categories of drugs is explained by shared A, C, and E factors that influence abuse of all drugs, but the model does not constrain the 3 factors to influence drug abuse in the same way.

The common vulnerability model (or latent phenotype model) is a submodel of the single independent pathway model because it allows for influences from A, C, and E, but constrains the influences to affect co-occurrence in the same manner. That is, genetic influences promote the same pattern of co-occurrence that is promoted by family environmental and nonfamily environmental influences. This model is more parsimonious than the independent pathway model because fewer factors are free to vary independently. This model also allows for genetic, family environmental, and nonfamily environmental influences that may be specific to each individual category of drug.

The marijuana gateway model is a submodel of the common vulnerability or latent phenotype model because it also constrains genetic and environmental factors to influence co-occurrence in the same way. However, it further constrains the model by assuming that the shared genetic and environmental influences operate through their influence on marijuana abuse, which in turn influences the abuse of every other category of drug. The gateway model of drug abuse[35-37] presents a sequential theory of lifetime patterns of drug initiation in which cigarettes, alcohol, or marijuana represent phases in drug use that facilitate involvement with "harder" drugs.

Table 1. Lifetime Prevalence of *DSM-III-R* Substance Abuse and Substance Dependence Among 6744 Subjects*

Substances	Prevalence of Substance Abuse (99% CI)	Prevalence of Substance Dependence (99% CI)	Total
Marijuana†	0.6 (0.4-0.9)	6.6 (6.0-7.2)	**7.2**
Stimulants‡	0.2 (0.0-0.4)	4.2 (3.7-4.7)	**4.4**
Sedatives§	0.1 (0.0-0.2)	1.3 (1.0-1.6)	**1.4**
Heroin and opiates‖	0.0 (0.0-0.1)	1.0 (0.7-1.3)	**1.0**
Psychedelics¶	0.1 (0.0-0.2)	1.0 (0.7-1.3)	**1.1**

**Sample comprises 3372 pairs of male twins. CI indicates confidence interval. All values are expressed as percentages.*
†Includes hashish, bhang, and ganja.
‡Includes uppers, amphetamines, speed, "ice," cocaine, and crack.
§Includes barbiturates, sleeping pills, Seconal, Valium, Librium, tranquilizers, Quaaludes, and Xanax.
‖Includes codeine, Demerol, morphine, Percodan, methadone, Darvon, opium, and Dilaudid.
¶Includes LSD (lysergic acid diethylamide), mescaline, peyote, psilocybin, DMT (dimethyltryptamine), and PCP (phencyclidine).

alcohol may correlate highly with patterns of reinforcement from cocaine and opiates. Recent research[24] has suggested that long-term marijuana use may alter corticotropin releasing factor function in the limbic system in a manner similar to that of alcohol, cocaine, and opiates. There is also recent evidence[25] that opiates and marijuana may activate mesolimbic dopamine transmisson through the same opioid receptor.

In our analyses, we addressed several questions about genetic and environmental influences on drug abuse. The first question was descriptive: Within an individual, to what extent is there an association among abuse of different drugs? Twin data are not required to address this issue of phenotypic association. However, by comparing the cross-twin, cross-drug correlations separately for monozygotic and dizygotic twins, it is possible to draw inferences about the relative importance of genetic and environmental factors in accounting for co-occurring drug abuse. We can also investigate the extent to which genetic influences on drug abuse are shared across different categories of drugs or, alternatively, the extent to which genetic influences on drug abuse are unique to each category of drug. Parallel questions about family and nonfamily environmental factors are also addressed.

RESULTS

Approximately 10% (10.1%) of twins met the *DSM-III-R* criteria for abuse or dependence of at least 1 of the illicit drugs at some time during their lives. **Table 1** indicates that for every drug, the majority of individuals who met criteria for abuse also exceeded the higher severity threshold for dependence.

Table 2 contains the conditional probabilities for abuse of different drugs by an individual (within-individual probabilities). The first column identifies the index drug, and the cells with numerical values contain the probability that an individual who abused the index drug also abused the drug listed at the top of the column. **Table 3** contains additional information about the association of abuse between various drugs. Cells to the right side of the table contain the within-individual tetrachoric correlations between each pair of drug categories. Cells to the left side of the table contain the odds ratios quantifying the relationship of abuse of the various pairs of substances. Results presented in Tables 2 and 3 demonstrate that abusing 1 category of drug is associated with a substantially increased risk of abusing other categories of drugs. These data support the conclusion that there is a strong commonality that cuts across the various categories of drugs. However, these data also indicate that there is not perfect concordance between any pair of categories, indicating that there are influences unique to each type of drug and influences that are shared or common across all categories of drugs.

The next step was to use the pattern of associations within individuals and across twin pairs to assess mechanisms that could underlie the observed co-occurrence. This was accomplished by comparing the fit of alternative models (**Table 4**). The single independent pathway model ($\chi^2_{65} = 79.4$; $P = .11$) and the common vulnerability or latent phenotype model ($\chi^2_{73} = 88.3$; $P = .11$) could not be rejected, while the marijuana gateway model could be rejected ($\chi^2_{76} = 143.2$; $P = .000005$). Because the single independent pathway model did not cause a significant decrement in the fit of the model, there was no need to test a less parsimonious multiple independent pathway model. The common vulnerability model also remains a viable model ($\Delta\ \chi^2_8 = 8.9$ [88.3 – 79.4]; $P = .35$), using substantially fewer parameters than the single independent pathway model. Because the common vulnerability model was more parsimonious, the remaining analyses were based on it. Once a model is selected, calculations are performed to determine the relative contributions of genetic and environmental influences conditional on that model. Parameter estimates obtained using the common vulnerability model indicated that 31% of the variance for the shared or common vulnerability was caused by additive genetic effects, 25% by family environmental effects, and 44% by nonfamily environmental effects.

Using the common vulnerability model, a model that deleted drug-specific genetic effects provided an adequate fit to the data and a model that deleted drug-specific environmental effects provided an adequate fit to the data, but a model that deleted both was statistically rejected. That is to say, there is evidence for a family influence on the individual drugs in addition to the family influence that is shared or common to all drugs. However, we were not able to determine if this family influence is caused by genetic effects, the family environment, or both.

Table 5 contains the parameter estimates calculated using the common vulnerability model. The values in the first column indicate the total genetic variance for each illicit drug. The second column indicates the proportion of variability that is due to genetic influences specific to an individual drug category rather than shared across drugs. The other columns provide similar information about family environmental influences and nonfamily environmental influences. In general, the relative patterns in the proportions of variance of genetic, family environmental, and nonfamily environmental influences are similar across the 5 categories of drugs although the magnitudes vary somewhat.

Table 2. Within-Individual Conditional Probabilities of Abusing Another Drug Given Abuse of the Index Drug Among 6744 Subjects*

	Probability of Also Abusing				
Index Drug	**Marijuana**	**Stimulants**	**Sedatives**	**Heroin and Opiates**	**Psychedelics**
Marijuana	. . .	.31	.12	.07	.12
Stimulants	.52	. . .	.17	.11	.18
Sedatives	.63	.53	. . .	.20	.26
Heroin and opiates	.46	.44	.26	. . .	.14
Psychedelics	.80	.72	.32	.14	. . .

Sample comprises 3372 pairs of male twins. See footnotes to Table 1 for substance categories.

Table 3. Within-Individual Tetrachoric Correlations (Right) and ORs (With 95% CIs) (Left) Among Drug Abuse Categories*

	Marijuana	**Stimulants**	**Sedatives**	**Heroin and Opiates**	**Psychedelics**
Marijuana	. . .	0.71	0.67	0.52	0.77
Stimulants	19.5 (15.1-25.1)	. . .	0.70	0.60	0.79
Sedatives	25.2 (16.2-39.1)	30.1 (19.5-46.4)	. . .	0.64	0.71
Heroin and opiates	11.6 (7.7-18.7)	19.5 (12.0-31.8)	31.6 (17.6-56.7)	. . .	0.52
Psychedelics	59.5 (32.9-107.6)	68.1 (40.0-116.1)	47.1 (27.1-81.8)	18.0 (8.8-36.8)	. . .

Sample population comprises 3372 pairs of male twins. OR indicates odds ratio; CI, confidence interval. See footnotes to Table 1 for substance categories.

Table 4. Multivariate Structural Equation Models Assessing the Covariation Among Drugs of Abuse*

Models	χ^2	*df*	*P*	$\Delta\chi^2$†	*df*	*P*
Independent pathway	79.4	65	.11	. . .	. . .	. . .
Common vulnerability (latent phenotype)	88.3	73	.11	8.9	8	.35
Marijuana gateway	143.2	76	.000005	54.9	3	.00000000007
Common vulnerability without genetic influences specific to each drug	91.0	78	.15	2.7	5	.75
Common vulnerability without common environmental influences specific to each drug	88.9	78	.19	0.6	5	.99
Common vulnerability without genetic and common environmental influences specific to each drug	119.9	83	.005	31.6	10	.0005

See "Methods" section for further descriptions of models. Ellipses indicate data not applicable.
†*This value is obtained by subtracting the value for χ^2 in the second column for each submodel from the value for χ^2 for the model from which the submodel is derived.*

The pattern of unique influences tells a different story. Marijuana abuse was somewhat influenced by family environmental factors specific to marijuana abuse, whereas the influence of family environment on the other types of drug abuse was always expressed through the shared or common vulnerability (column 4 of Table 5). Marijuana abuse, stimulant abuse, and sedative abuse had small proportions of variance contributed by unique genetic factors, while abuse of psychedelic drugs had no unique genetic influence. Heroin abuse, however, had a large contribution from genetic factors that were not shared with other drugs (column 2 of Table 5). Heroin shared 50% of its total variance with the common vulnerability (shared variance can be calculated from Table 5 by subtracting the value for each specific variance parameter from each total variance parameter [eg, shared total variance for heroin: {0.54 – 0.38} + {0.13 – 0.0} + {0.33 – 0.12} = 0.50]); it was the only drug that did not share at least 60% of its total variance with the common vulnerability. The family environmental influences on heroin, psychedelics, stimulants, or sedatives are shared entirely with the common vulnerability. However, only 59% of the influence of the family environment on the abuse of marijuana is shared with the common vulnerability, and, therefore, 41% is unique to marijuana. (This can be calculated from Table 5 by dividing the specific family environmental variance [0.12] by the total family environmental variance [0.29].)

COMMENT

Our data demonstrate a relationship among abuse of different categories of illicit drugs. An individual who abuses one category of drug is more likely to abuse other categories of drugs. Heroin abuse had the largest amount of unique genetic variance (38%) and the least amount of shared genetic variance (16%) of any of the drugs. The low prevalence of heroin abuse and dependence resulted in a broad confidence interval. Each category of drug abuse had a similar proportion of family environmental influence that was shared with the common vulnerability. However, only marijuana abuse had a significant contribution from the family environment that was specific to marijuana.

Possible limitations of this study include questions about the validity of telephone interviews, generalizability of results, low prevalence of abuse of some drugs, and nonresponse bias. Face-to-face interviewing was not practical in the present study because of the large and geographically diverse sample. Gfroerer and Hughes[29] com-

Table 5. Proportions of Variance in Drug Abuse Variables From Multivariate Biometrical Modeling Using the Latent Phenotype Model*

Substance Categories	Total Genetic Variance	Specific Genetic Variance	Total Family Environmental Variance	Specific Family Environmental Variance	Total Nonfamily Environmental Variance	Specific Nonfamily Environmental Variance
Marijuana	0.33	0.11	0.29	0.12	0.38	0.06
Stimulants	0.33	0.09	0.19	0.00	0.48	0.14
Sedatives	0.27	0.05	0.17	0.00	0.56	0.26
Heroin	0.54	0.38	0.13	0.00	0.33	0.12
Psychedelics	0.26	0.00	0.21	0.00	0.53	0.15

**Parameter estimates derived from common vulnerability model. See footnotes to Table 1 for substance categories.*

pared the results of face-to-face interviews in the National Household Survey on Drug Abuse with those of a similar telephone interview performed for the Quick Response Survey. Lifetime prevalence of marijuana use among adults aged 35 and older was 19.1% in the face-to-face survey and 14.9% in the telephone survey; although the difference was not very large, it was statistically significant. Lifetime prevalence of cocaine use was 3.9% in the face-to-face survey and 3.1% in the telephone survey, a nonsignificant difference. Rohde et al[30] reported lower prevalence of substance abuse in telephone vs face-to-face interviews, but found very good agreement between the 2 methods ($\kappa = 0.73$). In another study,[31] the lifetime rates of drug abuse or dependence did not differ between subjects interviewed face-to-face (19.6%) or by telephone (17.7%). Telephone interviews may produce somewhat lower prevalence estimates than face-to-face interviews for some drugs, but the 2 techniques provide generally similar results.

Male veterans in this study were initially exposed to drugs in the late 1960s and early 1970s. Because the National Vietnam Veterans Readjustment Study[38] did not find differences between male Vietnam-era veterans and their civilian counterparts for lifetime prevalence of drug abuse or dependence, our results may apply to male nonveterans from the same age cohorts. The lifetime prevalence of drug dependence (as defined by the *DSM-III-R*) in our sample was 9.5%, while Warner et al[39] reported a lifetime prevalence of drug abuse of 10.8% among males aged 35 to 44 years in the National Comorbidity Survey, further supporting the generalizability of our findings to nonveteran males. Because our sample of veterans included only men, we do not know if our findings are applicable to women.

Conditional on the models examined and their assumptions, our results suggest that there is a shared or common liability factor that underlies the abuse of all 5 classes of substances. That is, there is some characteristic of the individual that imparts vulnerability to the abuse of all categories of drugs. We refer to this characteristic as the shared or common vulnerability (or latent phenotype). Moreover, this generalized risk is influenced by genetic factors, family environmental factors, and nonfamily environmental factors. The reason that the abuse of different categories of drugs are associated is that the same characteristics of the individual that put him at risk for abusing one type of drug, also put him at risk for abusing every other class of drug. However, not every category of drug is influenced to the same extent by the shared or common vulnerability.

The common vulnerability model assumes that genetic, family environmental, and nonfamily environmental factors each produce the same pattern of co-occurrence among the categories of drugs. This contrasts with the independent pathway model, which allows genes to promote one pattern of co-occurrence, while environmental factors promote a different pattern. Our results also indicate that a single common vulnerability is sufficient to explain the patterns of association among the different categories of drugs. It might seem plausible that one characteristic would put an individual at greater risk for abusing sedatives and opiates while another characteristic would impart a shared risk for the abuse of marijuana and psychedelic drugs.

Are different drugs abused for different reasons? Our data support both affirmative and negative answers. The reason the risks for abusing the various drugs are highly correlated may be that there are genetic factors, family environmental factors, and nonfamily environmental factors that impart a risk that is applicable to the abuse of all of the drugs. The reasons abuse of different drugs fails to co-occur perfectly varies from drug to drug. Most of the genetic influence on heroin abuse is specific to heroin and not shared with other drugs, while most of the genetic influence on abuse of marijuana, stimulants, and sedatives is shared across drugs with a modest amount of genetic variance that is specific to each substance. The family environment influences co-occurrence among all categories of drugs. For marijuana abuse, there is an influence from the family environment that specifically influences marijuana abuse and no other drug category, while the other categories of drug abuse have no influence from the family environment that is not shared across all categories of drugs. That is, the family environment has no specific effect on abuse of stimulants, sedatives, heroin, or psychedelics. Something about the family environment imparts a substantial risk for all categories of drug abuse. Something else about the family environment imparts a specific risk for marijuana abuse. The nonfamily environment imparts a meaningful proportion of the risk for substance abuse that is shared across all categories of drug, as well as being specific to each category.

Future studies that address the causes of drug abuse should focus on social, psychological, and biological factors that influence the risk for abuse of every drug category. Our results also support the search for social, psychological, and biological factors that are unique to use of each category of drug, especially heroin. Molecular genetic studies of illicit drug abusers should consider classi-

fying individuals who abuse any 1 or more categories of drugs as having the affected phenotype.

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