

Illicit Psychoactive Substance Use, Heavy Use, Abuse, and Dependence in a US Population-Based Sample of Male Twins

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Background: In order to develop informed approaches to prevention and treatment of illicit psychoactive substance use, abuse, and dependence, we need to understand the sources of individual differences in risk.

Methods: In personal interviews with 1198 male-male twin pairs (708 monozygotic and 490 dizygotic) ascertained from a population-based registry, we assessed lifetime use, heavy use, and abuse of and dependence on cannabis, sedatives, stimulants, cocaine, opiates, and hallucinogens. Twin resemblance was assessed by probandwise concordance, odds ratio, tetrachoric correlations, and biometrical model fitting.

Results: Twin resemblance for substance use, heavy use, abuse, and dependence was substantial, and consistently greater in monozygotic than in dizygotic twins. For any drug use and for cannabis and hallucinogen use,

model fitting suggested that twin resemblance was due to both genetic and familial-environmental factors. Twin resemblance for sedative, stimulant, cocaine, and opiate use, however, was caused solely by genetic factors. With 2 exceptions (cocaine abuse and stimulant dependence), twin resemblance for heavy use, abuse, and dependence resulted from only genetic factors, with heritability of liability usually ranging from 60% to 80%. No consistent evidence was found for violations of the equal environment assumption.

Conclusions: In accord with prior results in studies of women, the family environment plays a role in twin resemblance for some forms of substance use in men. However, twin resemblance for heavy use, abuse, and dependence in men is largely caused by genetic factors, and heritability estimates are high.

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ILLICIT PSYCHOACTIVE substance use, abuse, and dependence are major public health problems. To develop informed approaches to prevention and treatment, we need to understand the sources of individual differences in risk. Substantial evidence suggests that the liability to psychoactive substance use disorder (PSUD) aggregates in families.¹⁻⁶ Both twin⁷⁻¹⁰ and adoption¹¹⁻¹³ studies suggest that part of this familial aggregation is due to genetic factors.

In the first phase of a comprehensive study of PSUD in a US population-based twin population, we examined cannabis, cocaine, hallucinogen, opiate, sedative, and stimulant use, abuse, and dependence in personally interviewed members of more than 800 female-female twin pairs.¹⁴⁻¹⁶ In a separate and recently completed study, we have interviewed personally, with the same assessment instrument, both members of 1193 male-male (MM) pairs ascertained from the same twin registry. In this article,

therefore, we examine the results for the use, heavy use, and abuse of and dependence on these categories of psychoactive substances in these MM pairs.

RESULTS

POTENTIAL BIASES

Noncooperation of the cotwin predicted an increased risk for psychoactive substance use, heavy use, abuse, and dependence in the twin in 10 of 56 analyses. For MZ twins, it predicted sedative use; sedative, stimulant, and opiate heavy use; cocaine abuse; and cocaine and opiate dependence. For DZ twins, it predicted sedative use and marijuana and sedative dependence. Although the findings were replicated across zygosity groups only once (for sedative use), these many significant findings—all in the same direction—were unlikely to occur by chance ($P = .005$).²⁴

Controlling for zygosity, the similarity of childhood and adult environments

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SUBJECTS AND METHODS

SUBJECTS

This report is based on data collected in the second wave of interviews in a new study of adult twins from the Virginia Twin Registry (now part of the Mid-Atlantic Twin Registry). The Virginia registry was formed by a systematic search of all Virginia birth certificates since 1918. Subjects from multiple births are matched by names and birth dates from state records to obtain addresses and telephone numbers. Twins were eligible for participation in this study if one or both twins were successfully matched, were members of a multiple birth that included at least 1 male, were white, and were born between 1940 and 1974. Of 9417 individuals eligible for the first wave, 6814 (72.4%) had completed interviews, 1163 (12.4%) refused, 33 (0.4%) had incomplete interviews, 388 (4.1%) did not agree within the study time limit, 862 (9.1%) could not be located, and 157 (1.7%) were deceased or too ill to be interviewed. At least 1 year after the completion of the first-wave interview (performed by telephone in most instances), we contacted the twins again and attempted to schedule a second-wave interview. The number of subjects eligible for wave-2 interviews included the 6814 with complete wave-1 interviews as well as 3 subjects interviewed at wave 2 who were eligible at wave 1 but from whom completed wave-1 interviews were not obtained. Whenever possible, this interview was completed face-to-face (79.4% of sample). Of the 6817 individuals eligible for the wave-2 interview, 5629 (82.6%) were successfully interviewed while 852 (12.5%) refused, 22 (0.3%) had incomplete interviews, 237 (3.5%) did not agree within the study time limit, 51 (0.7%) could not be located, and 26 (0.4%) were deceased or too ill to be interviewed. To assess the test-retest reliability of our assessments, 131 members of MM twins were reinterviewed 4.4 ± 1.1 months (mean \pm SEM) after their initial interview.

The current report is based on 1198 MM pairs with complete data on PSUD from the wave-2 interview. There were 1184 male-male twins, with 12 pairs from 4 all-male triplet births and 1 pair each from a male-male-female triplet birth and a male-male-female-female quadruplet birth. In addition, this sample includes 534 subjects whose cotwins did not complete a wave 2 interview, of whom 247 came from monozygotic (MZ) and 287 from dizygotic (DZ) pairs.

At the time of second-wave interview (1994-1998), subjects were 20 to 58 years old (mean [SD], 36.8 [9.1]),

and had a mean of 13.4 years of education (SD, 2.6). Interviewers had a master's degree in a mental health-related field or a bachelor's degree in this area plus 2 years of clinical experience. They received 40 hours of classroom training plus regular individual and group review sessions. Two senior staff reviewed each interview for completeness and consistency. Members of a twin pair were interviewed by different interviewers who were blind to clinical information about the cotwin.

ZYGOSITY DIAGNOSIS

We began assessing zygosity by genotyping 227 twin pairs with 8 or more highly polymorphic DNA markers. Using these pairs, we developed a Fisher discriminant function with PROC DISCRIM in SAS¹⁷ using height, weight, 6 standard zygosity questions, and the twins' history of any blood tests. Using this discriminant function, we could confidently assign zygosity to all of the remaining sample (operationalized as an estimated probability of monozygosity of $\leq 10\%$ or $\geq 90\%$) except for 97 pairs. Of these, we had usable DNA from both members of 65 pairs, from which we obtained zygosity. All available information on the remaining 32 cases, including photographs, was reviewed by 2 of us (K.S.K. and C.A.P.), who assigned final zygosity. Assignment of zygosity for twins without an interviewed cotwin was done using the discriminant function analysis. These analyses were based on 708 complete MZ pairs and 490 complete DZ pairs.

MEASURES

Lifetime use, heavy use, abuse, and dependence were assessed separately for 7 categories of substances using an adaptation of the Structured Clinical Interview for DSM-III-R.¹⁸ With illustrative specific forms, these categories were cannabis (marijuana and hashish); sedatives (quaalude, Seconal, and Valium); stimulants (speed, ecstasy, and Ritalin); cocaine (intranasal, freebase, and crack); opiates (heroin, Demerol [meperidine hydrochloride], morphine); hallucinogens (lysergic acid diethylamide, mescaline, and phencyclidine); and "other," including inhalants (glue and nitrous oxide), over-the-counter medications (diet and sleeping pills), and miscellaneous (steroids and poppers). For those substances that could be legally obtained, we told respondents that we were interested solely in nonmedical use, defined as use (1) without a physician's prescription; (2) in greater amounts than prescribed; (3) more often than prescribed; or (4) for any other reason than that a physician said they should be taken. Heavy

significantly predicted twin resemblance 7 out of 56 times: (1) For childhood environment, it predicted stimulant and hallucinogen use, cannabis, and any heavy use. (2) For adult environment, it predicted cocaine heavy use, hallucinogen abuse, and sedative dependence. Although there was no replication across substances or levels of use or misuse, this number of significant findings would occur by chance approximately 2% of the time,²⁴ and all the significant effects were in the predicted direction.

For most drug use categories, rates were higher in DZ than MZ twins. Although these differences were usu-

ally modest, they reached significance for cannabis use and abuse; sedative abuse; opiate heavy use; hallucinogen use; and any use, heavy use, and abuse.

TEST-RETEST RELIABILITY

Drug use was assessed with excellent reliability ($\kappa > 0.70$ and $r > 0.90$ for all), as was heavy use except with sedatives (**Table 1**). The test-retest reliabilities for drug abuse and dependence (where available) were in the fair to good range (most κ values between 0.50 and 0.70 and most r values > 0.80).

use was defined as ever using the substance more than 10 times per month.

Drug abuse and dependence were diagnosed using DSM-IV criteria,¹⁹ except that we ignored criterion B for substance abuse, which rules out abuse in the presence of dependence. Thus, we diagnosed abuse and dependence non-hierarchically. Use and misuse of the *other* category were too rare to usefully analyze separately, but the *other* category was added to the category of any PSUD.

STATISTICAL ANALYSIS

We assess twin resemblance in 3 ways. First, proband concordance is the proportion of affected individuals among cotwins of affected twins. This statistic ignores information from pairs in which both twins are unaffected. Second, the odds ratio (OR) reflects the risk of being affected (or using a substance) among cotwins of affected twins compared with the risk of being affected among cotwins of unaffected twins.

Third, we use a liability-threshold model to estimate the genetic and environmental contributions to twin resemblance for substance use, abuse, and dependence. For categorical characteristics, such as lifetime use or dependence, the estimates reflect resemblance in twins pairs for their liability to develop the disorder.²⁰ Liability is assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold expressing the disorder.

Individual differences in liability are assumed to arise from 3 sources: additive genetic (A), from genes with allelic effects that combine additively; common environment (C), which includes all sources shared by members of a twin pair, including family environment, social class, schools; and specific environment (E), which includes all remaining environmental factors not shared within a twin pair plus measurement error. Monozygotic twins within a pair resemble one another because they share all of their A and C components, while DZ pairs share (on average) half of their A and all of their C components. It is possible to include nonadditive genetic effects, such as dominance or epistasis, but these have not been implicated in prior studies of PSUD and their inclusion did not improve the fit of our models, so we did not consider them further.

Our model also assumes independence and additivity of the 3 components and the equality of shared environmental effects. The equal environment assumption requires that MZ and DZ pairs be equally similar in the etiologically relevant aspects of their shared environments. To test this assumption, we assessed twin similarity for

for environmental exposure in childhood using standard questions.²¹ Similarity of their adult environment is assessed by measures of current frequency of contact. We examine whether, when controlling for zygosity, pairs with greater environmental similarity are more similar for substance use, heavy use, abuse, or dependence.

Since drug use, abuse, and dependence are correlated in twin pairs, twin studies provide a method for detecting cooperation bias. If, for example, drug use predicts non-cooperation, then drug use in one twin should predict a decreased probability that the cotwin would be successfully interviewed.

Traditional twin modeling examines only pairs concordant for assessment. However, information about diagnostic thresholds is contained in twins whose cotwin was not interviewed. Using a recently developed option in the software package Mx,²² we fitted models including single twins by the method of maximum likelihood. During optimization, trial values of the parameters were used to generate an overall predicted covariance matrix and an overall matrix of thresholds. For any particular observation, the overall matrix was filtered to create a submatrix matching those observations that were present. Likewise, the corresponding subset of the matrix of thresholds is created. These matrices are then used to compute the log-likelihood of the observation in question. The log-likelihoods of all cases were summed to obtain the log-likelihood of the sample, which was maximized using numerical optimization software.

Maximum likelihood analysis of raw ordinal data does not directly provide an overall test of goodness of fit of the model. However, it is possible to perform such a test by comparing the fit of the model being used with the sum of the fits of models (MZ and DZ fitted separately) in which every correlation and every threshold are estimated as free parameters. Twice the difference in log-likelihood between this saturated model and the model being tested yields a statistic that is (under certain regularity conditions) asymptotically distributed as χ^2 values with degrees of freedom equal to the difference in the number of parameters in the 2 models. Tests between alternative models may be carried out the same way.

Alternative models are evaluated by comparing the difference in their χ^2 values relative to the difference in their degrees of freedom, according to the principle of parsimony—models with fewer parameters are preferable if they do not provide significantly worse fit. We operationalized parsimony by using the Akaike information criterion (AIC) statistic,²³ calculated as $\chi^2 - 2 df$, where df indicates degrees of freedom.

PREVALENCES AND PATTERNS OF TWIN RESEMBLANCE

Table 2 presents, for MZ and DZ twins, the prevalence, probandwise concordance, OR, and difference in ORs between zygosity for the use, heavy use, and abuse of and dependence on any illicit substance and for the 6 specific classes of illicit substances. The following results are noteworthy: (1) Prevalences of the various drug use categories differ widely. Rates for cannabis are consistently the highest and opiates among the lowest. (2) Across the various substances, abuse is usually more fre-

quently reported than heavy use, while dependence is substantially rarer. (3) In MZ twins, ORs were significantly greater than 1 for all categories of use; all categories of heavy use and abuse except opiates; and all categories of dependence except sedatives, opiates, and hallucinogens. For DZ twins, ORs significantly exceeded unity for all forms of use except opiates; for cannabis, stimulant, and cocaine heavy use; for cannabis and cocaine abuse; and for cocaine dependence. (4) In MZ twins, higher ORs were consistently seen for heavy use and abuse than for use. This trend was less clear in DZ twins. (5) Odds ratios were estimable in both MZ and DZ twins in 20 sub-

Table 1. Test-Retest Reliability of Psychoactive Substance Use, Heavy Use, Abuse, and Dependence (n = 131)*

Substance	Use		Heavy Use		Abuse		Dependence	
	κ	r	κ	r	κ	r	κ	r
Cannabis	+0.91	0.99	+0.84	0.98	+0.67	0.89	+0.60	0.89
Sedatives	+0.79	0.97	+0.39	0.79	+0.51	0.82
Stimulants	+0.72	0.92	+0.72	0.95	+0.60	0.92	+0.66	0.94
Cocaine	+0.93	0.99	+0.72	0.95	+0.68	0.92	+0.47	0.80
Opiates	+0.74	0.96	+0.66	0.94	+0.49	0.86
Hallucinogens	+0.88	0.99	+0.59	0.91
Any	+0.89	0.99	+0.74	0.93	+0.65	0.89	+0.63	0.92

*Ellipses indicate that fewer than 4 individuals met the criteria on either occasion of measurement.

stance category combinations. The OR was greater in MZ twins in all 20 categories and this difference was significant in 18. The 2 categories in which MZ resemblance did not significantly exceed DZ resemblance were cannabis use and cocaine abuse.

TETRACHORIC CORRELATIONS

As with the ORs, the tetrachoric correlations were consistently higher in MZ than in DZ twins (**Table 3**). With 2 exceptions (sedative heavy use and stimulant dependence), tetrachoric correlations in MZ twins exceeded 0.55, indicating a high degree of twin resemblance. Tetrachoric correlations in DZ twins were more variable, ranging from nearly 0 for opiate use and sedative abuse to greater than 0.40 for stimulant use, marijuana heavy use, and cocaine heavy use and abuse.

MODEL-FITTING RESULTS

Use

For model fitting, we will describe the results in each category for cannabis, as it is the most commonly used substance and provides, therefore, the greatest statistical power. We comment more briefly on results for other substances. For use, the full or ACE model fit moderately well for cannabis ($\chi^2_3 = 7.40, P = .06$). Compared with this model, we could reject, by the χ^2 difference test, the AE ($\chi^2_1 = 7.43, P = .006$); CE ($\chi^2_1 = 5.41, P = .02$); and E-only models ($\chi^2_2 = 218.67, P < .001$). The best-fit ACE model, which produced the lowest AIC value, suggested that one third of the variance in liability to cannabis use was due to additive genetic factors, one third to family environment, and one third to unique environment.

Similar results were found for any substance use and hallucinogen use. For both these categories, the AE and CE models could be rejected at or nearly at the .05 level and the E-only model could be rejected at the .0001 level. From the best-fit ACE model, family environment was seen to account for approximately 35% of the variance in liability, while genetic factors were considerably more important for hallucinogens than for any drug use.

For sedative, stimulant, cocaine, and opiate use, however, the best-fit model was the simple AE model, with the heritability of liability to use being estimated in the range of 50% to 70%. Against the ACE model, the CE

models could be rejected at the .05 level and the E-only models at the .0001 level for all these substances. It is noteworthy that in models containing both A and C, the positive correlation of these parameter estimates produces quite large confidence intervals (CIs). That is, when there is evidence of an effect of both genes and family environment for a dichotomous trait like substance use, even with relatively large sample sizes, parameter estimates for these 2 factors are known with little precision. In AE models, by contrast, the CIs are narrower.

Heavy Use

The results for heavy use of cannabis differed substantially from those for use. The full model fit well ($\chi^2_3 = 5.81, P = .12$). Against the ACE model, the AE model could not be rejected ($\chi^2_1 = 1.26, P = .26$), but both the CE ($\chi^2_1 = 18.79, P < .001$) and E-only ($\chi^2_2 = 203.87, P < .001$) models could be strongly rejected. The best-fit model was AE, with an estimated heritability of liability to cannabis heavy use of 84%. The absence of twin pairs concordant for opiate heavy use, abuse, or dependence made model fitting impossible. For heavy use of all other substances and any substance, the AE model provided the best fit, with estimated heritabilities that ranged from 45% for sedatives to 83% for any substance. The CE model could be rejected against the ACE model at the .05 level only for stimulant and any substance. The E-only model could be rejected for stimulants, cocaine, and any substance. The low prevalence of sedative and hallucinogen heavy use resulted in heritability estimates with wide CIs.

Abuse

Results for cannabis abuse resembled those seen for heavy use. While the AE model gave the same fit as the ACE model, the CE ($\chi^2_1 = 20.22, P < .001$) and E-only ($\chi^2_2 = 158.64, P < .001$) models could be rejected with high levels of statistical confidence. The heritability estimated from the best-fit AE model was high (76%), with a relatively narrow CI. Qualitatively similar results were obtained with abuse of any substance, as well as abuse of sedatives, stimulants, and hallucinogens. For all of the categories, both the CE and E-only models could be rejected against the ACE model by the χ^2 difference test. The rarer the rates of abuse, the broader were the CIs around the parameter estimates of the best-fit models.

Table 2. Prevalence, Probandwise Concordance, and Odds Ratios for Illicit Psychoactive Substance Use, Heavy Use, Abuse, and Dependence in Monozygotic (MZ) and Dizygotic (DZ) Twins*

Substance	Prevalence ± SE		Probandwise Concordance ± SE		Odds Ratio (95% CI)		Difference in Odds Ratios	
	MZ	DZ	MZ	DZ	MZ	DZ	χ^2 (df = 1)	P
Use								
Cannabis	50.4 ± 1.3	55.9 ± 1.8	0.73 ± 0.01	0.71 ± 0.02	7.5† (5.4-10.5)	4.2† (2.9-6.2)	0.95	.33
Sedatives	10.1 ± 0.8	11.5 ± 1.0	0.44 ± 0.03	0.25 ± 0.03	11.7† (6.7-20.6)	3.1† (1.6-6.3)	8.57	.003
Stimulants	17.7 ± 1.0	19.8 ± 1.3	0.52 ± 0.03	0.40 ± 0.03	9.5† (6.1-14.9)	3.9† (2.4-6.4)	7.00	.008
Cocaine	16.0 ± 1.0	18.2 ± 1.2	0.52 ± 0.03	0.36 ± 0.03	11.0† (6.9-17.5)	3.4† (2.0-5.7)	11.22	.001
Opiates	5.9 ± 0.6	6.0 ± 0.8	0.29 ± 0.04	0.07 ± 0.02	8.9† (4.1-19.2)	1.2 (0.3-5.1)	6.78	.009
Hallucinogens	12.9 ± 0.9	16.4 ± 1.2	0.62 ± 0.03	0.45 ± 0.03	26.7† (15.5-46.0)	6.7† (3.9-11.5)	12.82	<.001
Any	52.6 ± 1.3	59.0 ± 1.6	0.74 ± 0.01	0.73 ± 0.02	6.8† (4.9-9.4)	4.2† (2.8-6.1)	3.55	.06
Heavy Use								
Cannabis	14.5 ± 0.9	17.2 ± 1.2	0.63 ± 0.03	0.41 ± 0.03	26.2† (15.5-44.2)	5.2† (3.0-8.7)	18.87	<.001
Sedatives	1.1 ± 0.3	2.0 ± 0.5	0.13‡ ± 0.06	0.00‡	15.4† (1.6-145.5)	...	2.60	.11
Stimulants	4.0 ± 0.5	5.6 ± 0.7	0.36 ± 0.05	0.15 ± 0.04	20.7† (8.3-51.2)	3.2§ (1.0-10.0)	6.96	.008
Cocaine	3.0 ± 0.5	3.7 ± 0.6	0.42 ± 0.06	0.22 ± 0.05	40.4† (14.4-113.9)	9.4† (2.7-32.0)	3.32	.07
Opiates	0.8 ± 0.2	2.0 ± 0.5	0.00‡	0.00‡
Hallucinogens	0.8 ± 0.2	1.5 ± 0.4	0.18 ± 0.09	0.00‡	38.8¶ (3.5-428.1)	...	3.22	.07
Any	16.3 ± 1.0	19.8 ± 1.3	0.63 ± 0.03	0.43 ± 0.04	22.5† (13.7-36.8)	4.7† (2.9-7.7)	19.76	<.001
Abuse								
Cannabis	16.6 ± 1.0	20.1 ± 1.3	0.58 ± 0.03	0.38 ± 0.03	15.0† (9.4-24.0)	3.2† (2.0-5.3)	20.23	<.001
Sedatives	2.3 ± 0.5	4.3 ± 0.7	0.24 ± 0.06	0.05 ± 0.02	18.1† (5.1-64.3)	1.2 (0.2-9.0)	7.01	.008
Stimulants	7.1 ± 0.7	8.7 ± 0.9	0.40 ± 0.04	0.16 ± 0.03	14.8† (7.4-29.3)	2.3 (1.0-5.6)	11.49	.001
Cocaine	4.6 ± 0.6	5.7 ± 0.7	0.31 ± 0.04	0.25 ± 0.04	13.4† (5.7-31.9)	7.1† (2.7-18.5)	0.96	.33
Opiates	1.5 ± 0.3	2.3 ± 0.5	0.00	0.00
Hallucinogens	3.3 ± 0.5	3.5 ± 0.6	0.34 ± 0.05	0.00	24.3† (8.8-67.0)	...	9.37	.002
Any	19.8 ± 1.1	23.6 ± 1.4	0.61 ± 0.02	0.42 ± 0.03	14.5† (9.3-22.5)	3.2† (2.1-5.1)	22.02	<.001
Dependence								
Cannabis	4.1 ± 0.5	4.4 ± 0.7	0.28 ± 0.04	0.09 ± 0.03	12.4† (4.9-31.4)	2.4 (0.5-11.1)	3.56	.06
Sedatives	0.4 ± 0.2	0.8 ± 0.3	0.33 ± 0.15	0.00	3.38	.07
Stimulants	2.1 ± 0.4	2.1 ± 0.5	0.13 ± 0.04	0.10‡ ± 0.05	8.5¶ (1.7-42.0)	5.6 (0.6-49.1)	0.09	.76
Cocaine	2.8 ± 0.4	3.1 ± 0.6	0.41 ± 0.06	0.13 ± 0.04	41.0† (14.0-120.2)	5.6§ (1.1-27.5)	4.56	.03
Opiates	0.4 ± 0.2	1.0 ± 0.3	0.00	0.00
Hallucinogens	0.5 ± 0.2	1.0 ± 0.3	0.29 ± 0.13	0.00	4.27	.04
Any	6.9 ± 0.7	8.6 ± 0.9	0.41 ± 0.04	0.24 ± 0.04	15.5† (7.8-30.8)	4.2† (1.9-9.4)	6.10	.01

*Ellipses indicate that the value was not calculated. CI indicates confidence interval.

†P < .001.

‡n ≤ 20.

§P < .05.

||n ≤ 10.

¶P < .01.

However, cocaine abuse was an exception to this pattern. Here, the tetrachoric correlation was only modestly greater in MZ than DZ twins (+0.61 vs +0.49). The full-model estimates of a^2 , c^2 , and e^2 were 32%, 32%, and 37%, respectively. The E-only model could be confidently rejected against the ACE model ($\chi^2_2 = 39.12$, $P < .001$), but neither the AE nor the CE model could be rejected ($\chi^2_1 = 1.51$, $P = .22$; and $\chi^2_1 = 0.94$, $P = .33$; respectively). Although the CE model produced the best fit by AIC, the fact that the fits of the AE and CE models were within 0.57 χ^2 units of each other suggested that we had little power to determine the contribution of genetic vs environmental factors to the familial resemblance for cocaine abuse.

Dependence

The findings for cannabis dependence resembled those obtained for cannabis heavy use and abuse. Against the

ACE model, the E-only model could be confidently rejected ($\chi^2_1 = 21.47$, $P < .001$) and the CE model could be rejected at marginal levels of significance ($\chi^2_1 = 3.42$, $P = .06$). By AIC, the AE model produced the best fit, with an estimated heritability of 58%. Because of its greater rarity, the CIs on heritability estimates for cannabis dependence are considerably larger than those seen for cannabis abuse.

For both any cocaine use and cocaine dependence, the pattern of results was similar and the CE models could be rejected at the .05 level against the ACE models ($\chi^2_1 = 6.68$, $P = .01$; and $\chi^2_1 = 4.90$, $P = .03$; respectively). Estimates of heritability were high (71% and 79%, respectively). Results were less certain for sedative, stimulant, and hallucinogen dependence. For all 3 substances, the E-only model could be rejected ($\chi^2_2 = 7.73$, $P = .02$; $\chi^2_2 = 5.98$, $P = .05$; and $\chi^2_2 = 6.34$, $P = .04$; respectively), supporting the evidence of aggregation of risk within twin pairs. For both sedative and hallucinogen

Table 3. Tetrachoric Correlations, Model Fitting, and Parameter Estimates of Best-Fit Model for Illicit Psychoactive Substance Use, Heavy Use, Abuse, and Dependence in Monozygotic (MZ) and Dizygotic (DZ) Twins*

Substance	Tetrachoric Correlations		Model Fit in χ^2 Units				Parameter Estimates for Full and Best-Fit Models (95% CI)			
	MZ	DZ	ACE†	AE‡	CE‡	E§	F, B	a^2	c^2	e^2
Use										
Cannabis	0.67	0.51	7.4	14.8	12.8	226.1	F, B	0.33 (0.05-0.60)	0.34 (0.10-0.58)	0.33 (0.26-0.40)
Sedatives	0.67	0.34	3.4	3.4	12.8	80.3	F	0.68 (0.25-0.77)	0.00 (0.00-0.38)	0.32 (0.24-0.45)
							B	0.68 (0.55-0.78)		0.32 (0.22-0.45)
Stimulants	0.67	0.45	4.9	6.5	11.9	133.9	F	0.47 (0.12-0.75)	0.21 (0.00-0.50)	0.33 (0.24-0.43)
Cocaine	0.69	0.40	3.3	3.6	14.5	127.3	F	0.61 (0.25-0.77)	0.09 (0.00-0.40)	0.30 (0.22-0.40)
							B	0.70 (0.61-0.78)		0.30 (0.22-0.39)
Opiates	0.55	0.03	3.5	3.5	8.9	26.1	F	0.52 (0.11-0.69)	0.00 (0.00-0.33)	0.48 (0.32-0.69)
							B	0.52 (0.31-0.68)		0.48 (0.32-0.69)
Hallucinogens	0.82	0.58	5.4	9.3	18.1	205.8	F, B	0.53 (0.23-0.85)	0.30 (0.00-0.57)	0.17 (0.11-0.17)
Any	0.64	0.51	6.9	15.1	10.6	199.3	F, B	0.27 (0.00-0.55)	0.38 (0.12-0.46)	0.36 (0.29-0.44)
Heavy Use										
Cannabis	0.83	0.51	5.8	7.1	24.6	209.7	F	0.66 (0.35-0.89)	0.18 (0.00-0.46)	0.17 (0.11-0.24)
							B	0.84 (0.77-0.89)		0.17 (0.11-0.23)
Sedatives	0.49	0.00	2.8	2.8	5.3	5.3	F	0.45 (0.00-0.82)	0.00 (0.00-0.40)	0.55 (0.18-0.98)
							B	0.45 (0.00-0.82)		0.55 (0.18-0.98)
Stimulants	0.69	0.28	1.7	1.7	8.3	38.4	F	0.70 (0.20-0.84)	0.00 (0.00-0.42)	0.30 (0.16-0.49)
							B	0.70 (0.51-0.84)		0.30 (0.16-0.49)
Cocaine	0.78	0.51	0.3	0.8	3.5	48.1	F	0.55 (0.00-0.90)	0.23 (0.00-0.74)	0.22 (0.10-0.41)
							B	0.80 (0.62-0.90)		0.20 (0.10-0.38)
Hallucinogens	0.63	0.00	4.0	4.0	5.7	8.1	F	0.62 (0.00-0.91)	0.00 (0.00-0.65)	0.38 (0.09-0.98)
							B	0.62 (0.02-0.91)		0.38 (0.09-0.98)
Any	0.81	0.50	4.9	6.1	24.6	215.3	F	0.65 (0.36-0.88)	0.17 (0.14-0.44)	0.18 (0.12-0.25)
							B	0.83 (0.76-0.88)		0.17 (0.12-0.24)
Abuse										
Cannabis	0.75	0.39	5.4	5.4	25.6	164.0	F	0.76 (0.42-0.82)	0.01 (0.00-0.31)	0.23 (0.17-0.33)
							B	0.76 (0.68-0.83)		0.24 (0.17-0.32)
Sedatives	0.61	0.03	10.8	10.8	15.3	23.0	F	0.59 (0.06-0.81)	0.00 (0.00-0.37)	0.41 (0.20-0.73)
							B	0.59 (0.27-0.80)		0.41 (0.20-0.73)
Stimulants	0.68	0.22	5.0	5.0	15.1	57.6	F	0.66 (0.30-0.77)	0.00 (0.00-0.29)	0.34 (0.22-0.50)
							B	0.66 (0.50-0.78)		0.34 (0.22-0.50)
Cocaine	0.61	0.49	2.6	4.1	3.5	41.7	F	0.32 (0.00-0.78)	0.32 (0.00-0.68)	0.37 (0.37-0.37)
							B		0.57 (0.40-0.70)	0.43 (0.30-0.60)
Hallucinogens	0.70	0.00	8.0	8.0	14.9	32.3	F	0.65 (0.24-0.82)	0.00 (0.00-0.34)	0.35 (0.19-0.58)
							B	0.65 (0.41-0.82)		0.35 (0.18-0.59)
Any	0.76	0.40	4.6	4.6	26.6	186.6	F	0.74 (0.42-0.83)	0.03 (0.02-0.31)	0.23 (0.17-0.31)
							B	0.77 (0.69-0.83)		0.23 (0.17-0.31)
Dependence										
Cannabis	0.59	0.20	4.0	4.0	7.4	25.5	F	0.58 (0.00-0.75)	0.00 (0.00-0.02)	0.42 (0.42-0.65)
							B	0.58 (0.35-0.75)		0.42 (0.26-0.66)
Sedatives	0.83	0.00	4.5	4.5	7.3	12.2	F	0.87 (0.00-0.99)	0.00 (0.00-0.80)	0.13 (0.01-0.68)
							B	0.87 (0.32-0.99)		0.13 (0.01-0.67)
Stimulants	0.43	0.34	1.9	2.1	2.0	7.9	F	0.22 (0.00-0.72)	0.21 (0.00-0.62)	0.57 (0.28-0.92)
							B		0.39 (0.08-0.64)	0.61 (0.36-0.92)
Cocaine	0.77	0.37	1.1	1.1	6.0	39.8	F	0.79 (0.09-0.90)	0.00 (0.00-0.62)	0.21 (0.17-0.28)
							B	0.79 (0.59-0.90)		0.21 (0.10-0.42)
Hallucinogens	0.80	0.00	4.1	4.1	6.5	10.4	F	0.79 (0.00-0.90)	0.00 (0.00-0.73)	0.21 (0.03-0.80)
							B	0.79 (0.20-0.97)		0.21 (0.04-0.80)
Any	0.69	0.39	4.1	4.2	10.8	68.2	F	0.65 (0.16-0.81)	0.05 (0.00-0.48)	0.29 (0.18-0.44)
							B	0.71 (0.57-0.82)		0.29 (0.18-0.43)

*A indicates additive genes; C, common or familial environment; E, individual specific environment; CI, confidence interval; F, full model; and B, best-fit model by Akaike information criteria. Results could not be estimated for opiate heavy use, abuse, or dependence because of the absence of concordant pairs.

†Using 3 df.

‡Using 4 df.

§Using 5 df.

||Best-fit model using Akaike information criteria.

dependence, c^2 was estimated at 0 in the ACE model, but the deterioration in fit from the ACE to CE models was modest ($\chi^2_1 = 2.76$, $P = .10$; and $\chi^2_1 = 2.36$, $P = .12$; respectively). For stimulant dependence, the full model produced estimates of a^2 , c^2 , and e^2 of 0.22, 0.21, and 0.57, respectively. The CE model produced the best fit by AIC, but the fact that the fits of the ACE, AE, and CE models were within 0.18 χ^2 units of one another indicated that we have little power to determine the source of familial resemblance for stimulant dependence.

COMMENT

The goal of this article was to determine the sources of individual differences in risk for the use, heavy use, and abuse of and dependence on illicit psychoactive substances in men from a US population-based twin sample.

How representative of US men were the twins assessed in this study? In 1996, during the data-collection phase of this study, the National Household Survey on Drug Abuse assessed lifetime psychoactive substance use in more than 18 000 individuals.²⁵ Using the age categories for non-Hispanic white males in their report (re-weighted to approximate the age distribution of our sample), the predicted lifetime rates for the 3 categories of drug use in which our data were most comparable were cannabis, 41.2%; cocaine, 14.7%; and hallucinogens, 13.5%. Weighted estimates for lifetime use and dependence in US males are also available from the National Comorbidity Survey, conducted from 1990 through 1992. They reported lifetime use (dependence) rates for categories similar to 5 of our 6 categories: cannabis, 51.7% (6.2%); sedatives, 14.0% (1.0%); stimulants, 18.4% (1.8%); cocaine, 19.5% (3.5%); and hallucinogens, 14.1% (0.7%). The rates found in our twin sample (Table 2) were nearly all within the range found in these 2 comparable epidemiologic studies. Consistent with other studies, which showed that twins do not differ from the general population in rates of psychopathologic conditions,²⁶⁻²⁸ these results suggest that our sample is likely to be broadly representative of US men.

Two large-scale general population twin studies of psychoactive substance use and misuse are particularly comparable with this study: the male Vietnam Era Twin Registry⁸ and female-female twin pairs previously studied from the Virginia Twin Registry.¹⁴⁻¹⁶ Results from the Vietnam Era Twin Registry were reported for a category closest to our definition of abuse.⁸ Uniformly, across substance categories, the Vietnam era sample produced lower levels of heritability and more evidence for family environment than found in our sample. For the comparable categories of any substance, cannabis, and hallucinogen abuse, the heritability values reported from the Vietnam era study were below the lower 95% CIs of our estimates. While these differences could be caused by many factors, the 2 cohorts differed substantially in mode of ascertainment (birth certificates vs both members inducted into the armed services). Furthermore, the Vietnam era sample may have had a unique historical experience of drug exposure.

Our results were more similar to those found in adult female-female twin pairs from the Virginia Twin Regis-

try.¹⁴⁻¹⁶ For example, in women, the best-fit models for cannabis use and abuse produced estimates of a^2 , c^2 , and e^2 of 0.40, 0.35, and 0.25 and 0.72, 0.0, and 0.28, respectively, close to the estimates for men (Table 3). Some differences were noteworthy. In women, we found strong evidence that family environment affected risk for cocaine and stimulant use.^{15,16} In men, by contrast, the evidence, while present for both cocaine and stimulant use (ie, DZ correlations greater than half the MZ correlations), was slight and the AE model fit best for both substances.

Our findings are also relatively similar to those recently reported from a treated sample of US twins. Like us, van den Bree et al⁹ found, in men, more evidence for familial-environmental effects on use than on abuse/dependence; heritability estimates for abuse and/or dependence were mostly in the range of 0.60 to 0.80. As in our study, a recent investigation of adolescent Virginia twins reports that family environment substantially influences the risk for use of marijuana or any illicit substance.²⁹

The results of this study should be interpreted in the light of 6 potential methodologic limitations. First, although our sample size was large, the numbers of twins with certain forms of heavy use, abuse, and especially dependence were small. As reflected by the large CIs of our model-fitting results, this sample was insufficient to determine, with high precision, the magnitude of the genetic and environmental effects for a number of subtypes of PSUD.

Second, as this sample was restricted to whites, it is not possible to extrapolate these results to other ethnic groups. Third, while our sample was derived from a population-based twin registry and our prevalences were in the range of those reported elsewhere, results suggested that for several categories of drug use and misuse, the final study sample was unlikely to be completely representative of the original twin population. This is consistent with prior evidence that individuals with substance abuse are somewhat less likely to cooperate in general population surveys.^{30,31} The impact of differential cooperation on the results from twin studies is complex and not entirely predictable,^{32,33} but underestimation of heritability is probably more likely than overestimation.³² Furthermore, our analyses using Mx software²² included twins whose cotwins were not interviewed, which eliminates some of the bias. Essentially, we used information on potential differences in the prevalence of PSUD in those twins with vs without a cotwin participating to obtain a better estimate of the prevalence of PSUD in the population. The method is a binary data maximum likelihood application of the "missing at random" principle expounded by Little and Rubin.³⁴

Fourth, we found higher rates of substance use and misuse in DZ vs MZ twins. This pattern of findings could result from "true" differences (eg, higher average cotwin social support in MZ vs DZ twins) and/or methodologic factors (higher MZ correlations for noncooperativity leading to more effective screening of MZ vs DZ pairs³²). From whatever cause, the differences were modest and unlikely to substantially influence the results obtained.

Fifth, we assessed PSUD in this sample with a single structured interview. In this design, unreliability is con-

founded with individual-specific environment³⁵ and produces a downward bias in estimates of heritability. We can roughly assess the magnitude of this problem by examining the tetrachoric correlations from our test-retest reliability study (Table 1). These suggest that with the possible exceptions of sedative heavy use and abuse and cocaine dependence, the magnitude of diagnostic error was insufficient to produce large downward biases in our parameter estimates. However, some of the estimates reported here for individual-specific environment undoubtedly reflect diagnostic unreliability.

Finally, the human twin study is a quasiexperimental method that cannot approach the methodologic rigor possible in controlled genetic experiments.³⁵ With a phenotype such as illicit substance use and misuse, which is strongly correlated with a range of social factors,^{36,37} it is a particular concern that excess environmental resemblance of MZ vs DZ twins might upwardly bias heritability estimates.³⁵ We found modest evidence for such an effect using standard measures of the correlated childhood and adult environments. To further evaluate this possible bias, we fitted structural equation models designed to detect and correct for the effects of the equal environment assumption³⁸ to the 7 conditions in which we found evidence for its violation. For sedative dependence, too few affected twins were available to permit stable model estimation. For the remaining 6 conditions, the proportion of variance in liability in the full model accounted for by the correlated environment averaged 7%. However, in all but one of these models, this correlated environmental factor could be set to 0 with an improvement in the model AIC. The one exception was frequency of adult contact and heavy cocaine use, for which, with the inclusion of a parameter reflecting equal environment assumption violations, the heritability of liability declined from 80% to 60%. It is unlikely that the overall results of this investigation were substantially biased by violations of the equal environment assumption.

These results reinforce a growing body of family,¹⁻⁶ twin,^{7-10,14-16,39,40} and adoption studies¹¹⁻¹³ that suggest that the risk for psychoactive substance use and misuse is substantially influenced by genetic factors. Our results also support the hypothesis that family environment is important at the stage of substance initiation. The magnitude of genetic influences on PSUD is striking and exceeds that seen in our sample for common psychiatric disorders, such as major depression,^{41,42} panic disorder,⁴³ and phobias.⁴⁴

The demonstration of genetic variance in risk is only the beginning rather than the conclusion of a research program. Of the many questions that can now be asked, 4 are noteworthy. (1) What are the pathways from genes to substance misuse and to what extent do they involve personality, psychopathologic processes, variations in metabolism, target receptors, and/or postreceptor mechanisms? (2) What is the relationship between the genetic and environmental factors that influence initiation vs subsequent misuse?⁴⁵ (3) How specific are genetic risks for the use and misuse of individual psychoactive substances?¹⁰ (4) What are the chromosomal locations of susceptibility genes for PSUD?⁴⁶

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