Comorbidity between alcohol dependence and illicit drug dependence in adolescents with antisocial behavior and matched controls

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Abstract

Background: Knowledge regarding the causes of comorbidity among substance use disorders can have significant impact on future research examining the etiology of these disorders. Unfortunately, the conclusions of past studies examining the comorbidity among substance use disorders are conflicting; some studies emphasize familial influences common to multiple substances, while others emphasize substance-specific influences. Discrepancies in results may reflect different analytical approaches or differences in the samples. Here, we examine the causes of comorbidity between alcohol dependence and illicit drug dependence in adolescents.

Methods: We ascertained a clinical sample of adolescents treated for antisocial behavior and substance use disorders and their siblings and a matched control sample. A model fitting approach was used to test 13 alternative hypotheses for the causes of comorbidity.

Results: The best supported hypothesis for the comorbidity between alcohol dependence and illicit drug dependence was a model hypothesizing that comorbid disorders are alternate forms of a single underlying liability. The next best fitting models were two of the correlated liabilities models (correlated risk factors and reciprocal causation).

Discussion: The results suggest that the best hypotheses explaining the comorbidity between alcohol and illicit drug dependence in adolescents are that alcohol dependence and illicit drug dependence are manifestations of a single general liability to develop substance dependence or that there are separate liabilities that are highly correlated.

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1. Introduction

Family and twin studies suggest that there are familial and genetic influences on problems with alcohol (Kaprio et al., 1987; McGue et al., 1992; Kendler et al., 1997b). Although less research regarding the etiology of illicit drug abuse and dependence has been conducted, several studies also suggest that there are familial and genetic influences on problems with illicit drugs (Gynther et al., 1995; Tsuang et al., 1996; van den Bree et al., 1998; Kendler et al., 1997a). Given these findings and the evidence of significant comorbidity among substance use disorders from epidemiological studies (Kessler et al., 1997), several family (Kendler et al., 1997a; Bierut et al., 1998; Merikangas et al., 1998), twin (Grove et al., 1990; Johnson et al., 1996; Pickens et al., 1995; True et al., 1999; Tsuang et al., 1998), and adoption studies (Cadoret et al., 1986; Cadoret et al., 1995) have tested whether there are common familial influences on substance use disorders.

Increasing knowledge regarding the causes of comorbidity among substance use disorders could have significant impact on future research examining the etiology of these disorders. The results of studies examining the causes of comorbidity are especially interesting to geneticists searching for specific genetic mechanisms underlying risk for substance use disorders. If
studies examining the causes of comorbidity among substance use disorders suggest the importance of substance-specific familial influences, the results would recommend the search for potential quantitative trait loci (QTL) or candidate genes for problems with specific substances. In contrast, if there are significant common familial influences on problems with different substances, the results would recommend the search for QTL or candidate genes that affect the common vulnerability underlying problems with different substances. Unfortunately, the conclusions of studies examining the causes of comorbidity among substance use disorders are conflicting; some studies assert that there are both substance-specific and common (i.e., non-substance-specific) familial influences (Bierut et al., 1998; True et al., 1999; Tsuang et al., 1998), while others emphasize the importance of substance-specific familial influences (Merikangas et al., 1998; Meller et al., 1988) or common familial influences (Kendler et al., 1997a; Cadoret et al., 1986; Cadoret et al., 1995).

Animal studies also have provided somewhat inconsistent evidence. For example, studies examining behavioral cross-sensitization and cross-tolerance provide some evidence that alcohol and illicit drugs act on overlapping neural mechanisms. Behavioral cross-sensitization has been reported between alcohol and nicotine (e.g., Fredrikssoon et al., 2000), cocaine (e.g., Itzhak and Martin, 1999), and morphine (e.g., Nestby et al., 1997), though it was not found with amphetamine (e.g., Nestby et al., 1997). Further, Lessov and Phillips (2003) showed that morphine- and cocaine-sensitized mice showed cross-sensitization to alcohol, whereas alcohol-sensitized mice did not show cross-sensitization to morphine or cocaine. Evidence of cross-tolerance also has been reported between alcohol and several other drugs, including nicotine (e.g., Schoedel and Tyndale, 2003), morphine (e.g., Fish et al., 2002), and gamma-hydroxybutyric acid (GHB; e.g., Gessa et al., 2000).

The studies that support the importance of substance-specific familial influences and those that support common familial influences have two important differences. The first is that different analytical methods were used. Two common analytical methods used in these studies are family prevalence analyses and biometric model fitting. In family prevalence analyses, studies compare the prevalence of disorders in the relatives of different proband types (e.g., probands with both disorders being examined versus probands with only one of the disorders). In biometric model fitting, alternative hypotheses are evaluated by examining the fit between observed data and expected data given each hypothesized model, and the model yielding the best or most parsimonious fit between the observed and expected data is chosen. Studies using these different methods have provided conflicting results, with studies examining the comorbidity between alcohol and illicit drug problems using family prevalence analyses finding evidence for substance-specific influences (Merikangas et al., 1998; Meller et al., 1988) and studies using biometric model fitting approaches finding evidence for common familial influences (Kendler et al., 1997a; True et al., 1999).

Another possible reason for the conflicting results is a difference in the samples examined. Studies that supported common familial influences on problems with different drugs examined problems with alcohol and illicit drugs in the general population (Kendler et al., 1997a; Cadoret et al., 1986, 1995), whereas studies that found substance-specific familial influences generally examined problems with alcohol and illicit drugs in clinical samples (Merikangas et al., 1998; Meller et al., 1988).

In the present study, we examined the etiology of comorbidity between alcohol dependence and illicit drug dependence in adolescents treated for severe antisocial behavior and substance use disorders and a matched control sample. We used the Neale and Kendler (1995) model fitting approach rather than family prevalence analyses for two main reasons. First, evidence from simulation studies assessing the validity of analytical approaches used to test the causes of comorbidity between two disorders suggest that the Neale and Kendler model fitting approach does a better job of discriminating the plausible comorbidity models from the rejectable comorbidity models than family prevalence analyses. A simulation study examining the validity of family prevalence analyses found that although some family prevalence analyses validly discriminate the alternative forms model from alternative hypotheses, none of the family prevalence analyses testing the correlated risk factors model or the three independent disorders model were valid (Rhee et al., 2003). In contrast, the Neale and Kendler model fitting approach discriminated five classes of models (i.e., the alternate forms model, the random multifactorial models, the extreme multifactorial models, the three independent disorders model, and the correlated liabilities models) reliably (Rhee et al., 2004). Second, the Neale and Kendler model fitting approach enables the examination of 12 other hypotheses explaining the causes of comorbidity in addition to the model hypothesizing common familial influences as the cause of comorbidity between two disorders (i.e., the correlated risk factors model). The present study is the first study to examine a wide range of alternative hypotheses for the causes of comorbidity between alcohol dependence and illicit drug dependence.

1.1. The Neale and Kendler comorbidity models

All of the Neale and Kendler (1995) comorbidity models are versions of the continuous liability threshold model (Carter, 1969, 1973) and assume that there is a continuous liability distribution of multiple genetic and environmental causes for a disorder. This assumption is a reasonable one for substance use disorders, given the previous evidence of the importance of both genetic and environmental influences on substance use disorders (Tsuang et al., 1996; van den Bree et al., 1998). Neale and Kendler considered a wide range of hypotheses, including models that differ in the primary versus secondary disorder, the number of liability distributions underlying the two disorders (i.e., one, two, or three), and the level at which the two disorders are related (i.e., at the level of latent liabilities or at the level of phenotypes). Detailed information regarding the Neale and Kendler comorbidity models is provided in Neale and Kendler (1995) and will not be repeated here. Below is a short description of the 13 Neale and Kendler comorbidity models.
1.1.1. Chance model. The chance model hypothesizes that comorbidity between two disorders occurs as a result of chance alone.

1.1.2. Alternate forms model. The alternate forms model hypothesizes that two disorders are comorbid because they are alternate manifestations of a single liability.

1.1.3. Multiformity models. There are six multiformity models, which hypothesize that being affected by either disorder increases the risk for having the other disorder. In the random multiformity and the extreme multiformity model, individuals with disorder A or B have an increased risk for having the other disorder. In random multiformity, the increased risk for comorbidity is a probability of p or r, and in extreme multiformity, individuals must cross a second, higher threshold in order to have both disorders. In random multiformity of A and extreme multiformity of A, only individuals with disorder A have the increased risk for comorbidity, and in random multiformity of B and extreme multiformity of B, only individuals with disorder B have the increased risk for comorbidity.

1.1.4. Three independent disorders model. The three independent disorders model hypothesizes that comorbidity between two disorders occurs because the comorbid disorder is a disorder that is separate from either disorder occurring alone.

1.1.5. Correlated liabilities models. There are four correlated liabilities models. The correlated risk factors model hypothesizes that two disorders are comorbid because the risk factors for the two disorders are correlated. The reciprocal causation model hypothesizes that comorbidity between two disorders occurs because A and B cause each other in a feedback loop. The A causes B model is a sub-model of the reciprocal causation model that hypothesizes that comorbidity between two disorders occurs because A causes B. The B causes A model is a sub-model of the reciprocal causation model that hypothesizes that comorbidity between two disorders occurs because B causes A.

In the correlated liabilities models, the causal processes take place at the liability. In the correlated risk factors model, the risk factors for the two disorders are correlated, whereas in the A causes B, B causes A, and reciprocal causation models, the risk factors are united into a common latent phenotype prior to causation. The correlated liabilities models are very different from the multiformity models, which suggest that the increased risk for the second disorder only occurs if an individual crosses a threshold on the liability and is affected by a disorder.

2. Methods

2.1. Participants

Data from a clinical sample and a control sample were analyzed jointly. The clinical sample consisted of 272 probands (7.0% female; age 13–20; mean age = 16.32; standard deviation of age = 1.24) from an adolescent residential or day treatment program for severe antisocial behavior and substance use disorders and the probands’ 362 siblings (45.9% female; age 11–25; mean age = 17.02; standard deviation of age = 3.30). All clinical probands were recruited from consecutive admissions to an unlocked residential or day treatment facility in the Denver metropolitan area, to which they had been referred by social service and/or juvenile justice agencies for serious antisocial behavior and substance use disorders. All probands in the present study had a full sibling between age 11 and 25. The ethnicity distribution for the clinical probands is 47.4% non-Hispanic Caucasian, 40.8% Hispanic, 8.1% African-American, 2.9% Native American, 0.4% Asian, and 0.4% unknown.

All clinical probands were referred to treatment for severe substance use disorders and met the criteria for substance abuse and/or substance dependence for one or more substances. Given that the present study’s focus is substance dependence, clinical probands who did not surpass the threshold for the presence of substance dependence and their siblings (30% of the clinical sample) were excluded from the analyses. The final sample size of the clinical sample was 191 probands and 253 siblings.

The control sample consisted of 283 “probands” (8.5% female; age 12–21; mean age = 16.53; standard deviation of age = 1.50) who were matched to the clinical probands by sex, age (±1 year), ethnicity, and zip code and their 422 siblings (45.0% female; age 11–25; mean age = 16.69; standard deviation of age = 3.38). The control sample was recruited via telephone queries by a marketing research company. Given that analyses are restricted to sibling pairs where the sibling is less than 25 years old, there is not a one-to-one correspondence between the control “probands” and the clinical probands in the current sample. The ethnicity distribution for the control “probands” is 58.3% non-Hispanic Caucasian, 34.3% Hispanic, 6.0% African American, and 1.4% Native American.

2.2. Procedure

Written informed assent (from minor participants) or consent (from adult participants or guardians of minor participants) was obtained after providing the participants with a complete description of the study. All assent/consent forms and research protocols were approved by the institutional review board of the University of Colorado. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1996) substance dependence symptoms were assessed by in-person interviews using the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM). The CIDI-SAM is a valid and reliable structured interview (Compton et al., 1996; Cottler et al., 1989; Crowley et al., 2001; Zanis et al., 1995) that assesses symptoms and diagnoses of abuse and dependence for alcohol and eight classes of illicit drugs (i.e., marijuana, opioids, sedative/hypnotics, inhalants, amphetamines, cocaine, hallucinogens, and phencyclidine). The CIDI-SAM has been used to assess substance use disorders in adolescents successfully (Thompson et al., 1996; Whitmore et al., 1997).
Table 1
Number of participants (%) with DSM-IV substance dependence diagnoses

<table>
<thead>
<tr>
<th></th>
<th>Clinical sample</th>
<th>Control sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proband</td>
<td>Sibling</td>
</tr>
<tr>
<td>None</td>
<td>81 (29.8%)</td>
<td>293 (80.9%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>90 (33.1%)</td>
<td>36 (9.9%)</td>
</tr>
<tr>
<td>Any illicit drug</td>
<td>178 (65.4%)</td>
<td>58 (16.0%)</td>
</tr>
<tr>
<td>Marijuana</td>
<td>160 (58.8%)</td>
<td>49 (13.5%)</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>49 (18.0%)</td>
<td>9 (2.5%)</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>39 (14.3%)</td>
<td>15 (4.1%)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>30 (11.0%)</td>
<td>10 (2.8%)</td>
</tr>
<tr>
<td>Opioids</td>
<td>8 (2.9%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>4 (1.5%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Sedative/hypnotics</td>
<td>2 (0.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Total number of participants</td>
<td>272</td>
<td>362</td>
</tr>
</tbody>
</table>

2.3. Analyses

We tested 13 alternative comorbidity models to examine the causes of comorbidity between alcohol dependence and illicit drug dependence (i.e., dependence on marijuana, opioids, sedative/hypnotics, inhalants, amphetamines, cocaine, hallucinogens, or phencyclidine). Analyses examining dependence on individual illicit drugs could not be conducted given the small number of participants with individual illicit drug dependence diagnoses (see Table 1).

An examination of substance dependence in adolescents must address the fact that the number of substance dependence symptoms for all substances increases significantly with age during adolescence and possible sex differences in the prevalence of substance dependence (Young et al., 2002). Therefore, rather than estimating a single threshold for the entire sample, we used an extension of the Neale and Kendler model fitting approach that allowed the threshold of each disorder for each individual to vary as a function of his or her age and sex. The formula for an individual’s threshold is: a threshold intercept parameter + (the age difference in threshold × the individual’s age) + (the sex difference in threshold × the individual’s sex). This formula reflects a linear change in threshold with age (which is equivalent to specifying a cumulative normal function for the probability of the disorder as a function of age), and different thresholds for males and females.

Neale and Kendler (1995) quantified the probabilities for the 16 combinations of affected or unaffacted status for pairs of relatives (e.g., neither disorder present in either relative, both disorders present in both relatives, etc.) for each comorbidity model and demonstrated a model-fitting approach to test each comorbidity model. In the Neale and Kendler model fitting approach, the observed data are the number of pairs in each possible combination of disease state for different types of relative pairs (e.g., both alcohol dependence and illicit drug dependence in siblings 1 and 2, illicit drug dependence only in sibling 1 and alcohol dependence only in sibling 2, etc.). The observed data are then compared to the numbers of pairs expected given the pairwise probabilities for each possible combination of disease state for the comorbidity model being tested.

In the present study, the alternative comorbidity models were tested by analyzing data from the clinical and control samples in a joint analysis. The inclusion of a clinical sample increases the power of the analyses while the inclusion of a control sample enables the estimation of population (unselected) thresholds rather than fixing them to predetermined estimates. The ascertainment in the clinical sample in the present study is single ascertainment, where probands have one disorder or both disorders being examined. There were no double-proband families, consistent with the probability of being ascertained given affected status (known as pi; Morton, 1982) being close to zero. Probands who have neither disorder are not included in the clinical sample; nor are their relatives. Data were analyzed using an ascertainment correction demonstrated by Rijsdijk et al. (1999), which corrects for the distortion of the expected frequencies resulting from this omission. In the correction, each expected proportion is divided by the sum of the expected proportions so that the expected proportions sum to one.

3. Results

Table 1 shows the number of participants with each of the DSM-IV substance dependence diagnoses in the clinical sample and the control sample. As expected, the number of participants with no dependence diagnosis is lowest in the clinical probands (clinical probands with no dependence diagnosis were removed from the analyses), intermediate in the siblings of the clinical probands, and highest in the control sample, while the number of participants with alcohol dependence and illicit drug dependence is highest in the clinical probands, intermediate in the siblings of the clinical probands, and lowest in the control sample.

Table 2 shows the model fitting results and the parameter estimates for models testing the causes of comorbidity between alcohol dependence and illicit drug dependence. The $-2 \log \text{likelihood} = -2 \ln L$ evaluates the discrepancy between the observed data and the data expected by the model. Models with lower $-2 \ln L$ fit the data better, and models with lower Akaike Information Criterion ($AIC = -2 \ln L - 2d.f.$) values indicate a more parsimonious fit, taking model complexity as well as fit into account.
Table 2
Model fitting results and parameter estimates (i.e., sibling correlation, thresholds, probability of being affected by the disorder, correlation between risk factors, causal parameters, and ascertainment probability for alcohol dependence only) from Neale and Kendler comorbidity models

<table>
<thead>
<tr>
<th>Model</th>
<th>−2ln $L$</th>
<th>d.f.</th>
<th>AIC</th>
<th>$r_s$</th>
<th>$t_1$</th>
<th>$t_2$</th>
<th>$r_s$</th>
<th>$t_1$</th>
<th>$t_2$</th>
<th>$p$</th>
<th>$r$</th>
<th>$r_{AB}$</th>
<th>$k_A$</th>
<th>$k_B$</th>
<th>$\alpha$</th>
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<td>CH</td>
<td>2700.12</td>
<td>666</td>
<td>1368.12</td>
<td>0.24</td>
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<td>-0.06</td>
<td>2.93</td>
<td>-0.08</td>
<td>-0.17</td>
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<td>0.58</td>
<td>0.22</td>
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<td></td>
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<td>2388.59</td>
<td>668</td>
<td>1052.59</td>
<td>0.37</td>
<td>3.31</td>
<td>-0.12</td>
<td>0.47</td>
<td>0.17</td>
<td>0.22</td>
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<tr>
<td>RM</td>
<td>2383.29</td>
<td>664</td>
<td>1055.29</td>
<td>0.34</td>
<td>4.03</td>
<td>-0.12</td>
<td>0.32</td>
<td>3.03</td>
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<tr>
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<td>665</td>
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<td>3.58</td>
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<td>1054.78</td>
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<td>3.58</td>
<td>-0.17</td>
<td>0.27</td>
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<td>0.20</td>
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<tr>
<td>ACB</td>
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<td>1055.47</td>
<td>0.33</td>
<td>3.62</td>
<td>-0.10</td>
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<td>3.01</td>
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<tr>
<td>BCA</td>
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<td>1056.13</td>
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<td>3.41</td>
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<tr>
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<td>3.08</td>
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<td>0.43</td>
<td></td>
<td></td>
<td></td>
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<td>0.17</td>
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</table>

Note. CH = chance; AF = alternate forms; RM = random multiformity; RMA = random multiformity of A; RMB = random multiformity of B; EM = extreme multiformity; EMA = extreme multiformity of A; EMB = extreme multiformity of B; TD = three independent disorders; CR = correlated risk factors; ACB = A causes B; BCA = B causes A; RC = reciprocal causation; $-2\ln L = -2 \log$ likelihood; d.f. = degrees of freedom; AIC = Akaike’s Information Criterion; $r_s$ = sibling correlation; $t_1$ = intercept parameter for first threshold (the age change in threshold per year and the sex difference in threshold appear in the second and third line, respectively); $t_2$ = intercept parameter for second threshold (the age change in threshold per year and the sex difference in threshold appear in the second and third line, respectively); $p$ = probability of having disorder A or B; $r$ = probability of having disorder A or B; $r_{AB}$ = correlation between influences shared between disorder A and B; $k_A = A$ causes B parameter; $k_B = B$ causes A parameter; $\alpha$ = ascertainment probability for alcohol dependence only given ascertainment probability for illicit drug dependence only equals 1.
In the present study, the best fitting model (i.e., the model with the lowest AIC) was the alternate forms model. Equal second were two of the correlated liabilities models: correlated risk factors and reciprocal causation. The results of a simulation study (Rhee et al., 2004) suggest that choosing the model with the lowest AIC as the best fitting model discriminates between alternate forms, multiformity, three independent disorders, and correlated liabilities models successfully. However, the difference in the AIC for the alternate forms model (1052.59) and the AICs for the next best fitting models (1054.70 for the reciprocal causation model and 1054.78 for the correlated risk factors model) is small, suggesting that both a model hypothesizing a single liability distribution for alcohol and drug dependence and a model hypothesizing two separate liability distributions that are highly correlated are viable models that cannot be rejected.

The age change in threshold per year (reported in the second line under column t1 or t2) suggests that in general, the prevalence of alcohol and illicit drug dependence increases with age. The sex difference in threshold (reported in the third line under column t1 or t2) suggests that in general, the prevalence of alcohol and illicit drug dependence is lower in females than in males.

The ascertainment parameter for alcohol dependence only ranged from 0.04 to 0.22 when the ascertainment probability for illicit drug dependence only was fixed to be equal to 1 (see Table 2). This means that the probability of being treated in this clinical sample and being ascertained as a participant in this study is 4.5–25 times higher for children with illicit drug dependence only than children with alcohol dependence only.

4. Discussion

We examined 13 alternative models explaining the causes of comorbidity in substance dependence in a clinical sample of adolescents with severe antisocial behavior and substance use disorders and a matched control sample. The present study is the first study to test a wide range of hypotheses regarding the causes of comorbidity between alcohol dependence and illicit drug dependence. It is also the first study to examine this issue in adolescents. The best fitting model explaining the comorbidity between alcohol dependence and illicit drug dependence was the alternate forms model. After the alternate forms model, the next best fitting models were two of the four correlated liabilities model, the correlated risk factors and reciprocal causation models, followed by two of the random multiformity models (random multiformity and random multiformity of A).

Although we could not establish any one model as the single correct explanation for the comorbidity between alcohol dependence and illicit drug dependence (as the fit of the alternative models was close), the best-fitting models strongly support the close overlap between the etiology of alcohol dependence and illicit drug dependence. The most likely hypotheses are that the comorbidity between alcohol dependence and illicit drug dependence exists because dependence symptoms for alcohol and illicit drugs are alternate manifestations of the same underlying liability or because the separate liabilities are strongly correlated (i.e., correlated risk factors or reciprocal causation). Although the alternate forms model and the correlated liabilities model seem to suggest two different conceptual conclusions (i.e., a single liability or two separate liabilities), the parameters from the correlated risk factors model suggest that if there are two separate liabilities, the correlation between them is high (i.e., 0.77 for the familial risk factors and 0.78 for the non-familial risk factors).

Intermediate in likelihood are the two causal models (i.e., alcohol dependence causes illicit drug dependence or illicit drug dependence causes alcohol dependence), and two of the multiformity models (random multiformity and random multiformity of alcohol dependence), which hypothesize that being affected by either disorder increases the risk for having the other disorder. Models with higher AICs and therefore unlikely hypotheses are the other multiformity models (random multiformity of B, extreme multiformity, extreme multiformity of A, extreme multiformity of B), the three independent disorders model (which hypothesizes a third, independent comorbid disorder), and the chance model (which hypothesizes that comorbidity occurs simply as a result of chance).

Our results conflict with previous findings of significant substance-specific familial influences (Bierut et al., 1998; Merikangas et al., 1998; True et al., 1999; Tsuang et al., 1998; Meller et al., 1988). One source of discrepancy is the difference in analytical methods (i.e., family prevalence analyses or biometric model fitting). However, the discrepancy between the present study’s results and previous studies’ support for significant substance-specific familial influences cannot be explained completely by differences in analytical methods. First, two studies using biometric model fitting also concluded that there are significant substance-specific familial influences (True et al., 1999; Tsuang et al., 1998). Second, several studies (Merikangas et al., 1998; Meller et al., 1988) have concluded that there are no common familial influences on different substance use disorders given the finding that having a family member with disorder A-only (e.g., alcohol dependence only) does not increase the risk for disorder B-only (e.g., drug dependence only); simulation results (Rhee et al., 2003) have shown that the alternate forms model cannot be the correct model for such results, sampling error notwithstanding.

There are several additional reasons for the discrepancy between the present study’s results and previous findings. First, there are notable differences in the ascertainment of the sample. The probands in the present study were recruited from a residential or day treatment center and may have more severe substance problems than participants in the previous studies, who were recruited from the general population (True et al., 1999; Tsuang et al., 1998), outpatient treatment centers (Merikangas et al., 1998), or either inpatient or outpatient treatment centers (Bierut et al., 1998). Second, the number of female probands and the number of probands with only a diagnosis of alcohol dependence were small in our sample. Most significantly, probands in our sample were referred to treatment by social service and juvenile justice agencies for both antisocial behavior and substance use disorders, whereas participants in the previous studies had not been referred for treatment of antisocial behavior. In the present study, liability common to the specific substance...
dependence diagnoses may reflect liability for antisocial behavior. Therefore, it is possible that probands in our sample may have a subtype of alcohol or drug dependence representing a single liability, and that our results may not generalize to substance use disorders existing without the presence of antisocial behavior. An important future direction is to test the Neale and Kendler models in a representative sample; simulation results from a study examining the validity of the Neale and Kendler model-fitting approach suggests that such a study will need to employ a very large sample (Rhee et al., 2004).

Second, our study examined substance dependence in adolescents, whereas previous studies examined substance use disorders in adults. The causes of comorbidity among substance use disorders may differ in adults and adolescents. The availability of different substances, the legal consequences of using different substances, and the degree of experimentation with different substances could be very different in adults and adolescents. For example, the examination of comorbidity between alcohol dependence and illicit drug dependence is the examination of two illegal drugs in United States adolescents, but it is an examination of one legal drug and one illegal drug in United States adults. Dick et al. (2001) found that the magnitude of genetic influences on alcohol use in adolescence is higher in urban areas than in rural areas, and they suggested that differences in the availability of alcohol in the two environments may be one of the reasons for the difference in the etiology of alcohol use in the two environments. Therefore, it is possible that dependence on two drugs similar in availability (e.g., alcohol and illicit drugs in adolescence) is a manifestation of the same underlying liability while dependence on two drugs dissimilar in availability (e.g., alcohol and illicit drugs in adulthood) reflects separate liabilities.

In conclusion, this first examination of a wide range of hypotheses for the causes of comorbidity among substance use disorders in adolescents suggests that symptoms of alcohol dependence and illicit drug dependence are manifestations of the same underlying liability or two very highly correlated liabilities. These results suggest that the search for specific genetic influences on substance dependence risk in adolescents should include the search for QTL or candidate genes influencing the common vulnerability underlying different substances of abuse. The results conflict with the conclusions of previous studies that found significant substance-specific familial influences on substance use disorders. This discrepancy suggests the possibility of heterogeneity in the causes of comorbidity between alcohol dependence and illicit drug dependence and that the present conclusions may be specific to antisocial substance dependence in adolescence.

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