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Ethnic Differences in Level of Response to Alcohol Between Chinese Americans and Korean Americans*

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Abstract

Objective—Koreans have higher rates of alcohol-use disorders and family history of alcoholism, compared with Chinese. These differences likely reflect both environmental and genetic influences. One genetically influenced characteristic that may contribute to these ethnic differences is level of response to alcohol. Variant alleles of aldehyde dehydrogenase (*ALDH2*) and alcohol dehydrogenase (*ADH1B*) genes are prevalent in individuals of Asian heritage and have been associated with an increased level of response to alcohol and a decreased risk for alcohol dependence. Additionally, a low level of response to alcohol is more common in individuals with a first-degree family history of alcoholism and is predictive of increased risk for this disorder. It also is possible that sociocultural factors have an impact on an individual's response to alcohol. The current study examined self-report level of response to alcohol, *ALDH2* and *ADH1B*, country of origin, and family history of alcoholism in 154 Chinese- and 181 Korean-American college students.

Method—Participants were evaluated via in-person interviews and genotyped at the *ALDH2* and *ADH1B* loci.

Results—Ethnicity was significantly related to level of response to alcohol, with Koreans having a lower self-reported level of response than Chinese. This relationship remained significant after considering the effects of gender, height, weight, quantity and frequency of alcohol consumption (over the previous 90 days), *ALDH2* genotype, *ADH1B* genotype, country of origin, and first-degree family history of alcohol dependence.

Conclusions—The results suggest that a low level of response to alcohol may contribute to the increased risk for alcohol abuse and dependence found in Koreans, relative to Chinese. More research is needed to determine additional factors that may be contributing to the low alcohol response and high rates of alcoholism in Koreans.

Individuals of asian descent comprise more than 50% of the total world population and approximately 4.4% of the population of the United States (Reeves and Bennett, 2003; World Gazetteer, 2006). Although Asians represent a diverse racial group with origins in many different countries, most epidemiologic studies on alcohol-use disorders (AUDs) conducted

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within the United States have aggregated Asian-American subgroups when making comparisons with other racial and ethnic groups. Despite their underrepresentation in national surveys, existing data indicate that Asian Americans, as a whole, have approximately half the rates of lifetime and past-year AUDs of other ethnic groups (Grant et al., 2004; Substance Abuse and Mental Health Services Administration, 2005; Zhang and Snowden, 1999).

A large cross-national epidemiologic study, however, found substantial differences in rates of AUDs between Asians from Taiwan and those from South Korea (Helzer et al., 1990). In Taiwan, the lifetime rate of AUDs was 7% (13% for men and 0.7% for women), whereas in South Korea it was 23% (43% for men and 3% for women). Consistent with these data, our laboratory found a lower rate of alcohol dependence among Chinese-American college students (5%), compared with Korean-American college students (13%) (Luczak et al., 2004).

Differences in rates of AUDs across these Asian subgroups likely reflect both environmental and genetic influences. Although the common practice is to treat ethnicity as a single variable on which groups meaningfully differ, this practice obscures the many interrelated sociocultural and biological factors that comprise it. Higher rates of abstinence and lower rates of alcoholism among individuals of Asian descent may owe, in part, to sociocultural factors (e.g., emphasis on drinking in moderation, social stigma regarding drunkenness).

In addition, biological factors may contribute to ethnic differences in rates of alcoholism. One potentially important biological characteristic is individual variability in level of response to alcohol, which is a genetically influenced trait (Heath and Martin, 1992; Martin et al., 1985; Neale and Martin, 1989). This trait has been proposed as a mediator, or endophenotype, of the genetic risk for alcoholism (Schuckit, 2000). Variability in level of response to alcohol has been associated with a positive family history of alcoholism. It may be particularly relevant to Asian populations, because they possess a high prevalence of variant alleles of two genes involved in alcohol metabolism that have been associated with alcohol dependence and level of response to alcohol.

Genes for aldehyde dehydrogenase (*ALDH2*; 12q24) and alcohol dehydrogenase (*ADH1B*; 4q22) have both been independently associated with decreased risk for alcohol dependence. A recent meta-analysis of studies involving Asians found that having one *ALDH2**2 (*ALDH2**Lys487) allele was associated with a four- to fivefold lower risk for alcohol dependence, and having two *ALDH2**2 alleles was related to an eight- to ninefold lower risk, compared with individuals with *ALDH2**1 (*ALDH2**Glu487) alleles (Luczak et al., 2006). In individuals without *ALDH2**2 alleles, having one *ADH1B**2 (*ADH1B**47His) allele was associated with approximately a fourfold reduction in the risk for alcohol dependence, and having two *ADH1B**2 alleles was associated with approximately a fivefold reduction in risk, compared with individuals with *ADH1B**1 (*ADH1B**47Arg) alleles. In individuals with one *ALDH2**2 allele, having one *ADH1B**2 allele was associated with about one-sixth the rate of alcohol dependence, and having two *ADH1B**2 alleles was associated with about one-eleventh the rate. Approximately 40% to 50% of Chinese, 30% of Koreans, and no Caucasians possess at least one *ALDH2**2 allele, and approximately 90% of both Chinese and Koreans and roughly 5% of Caucasians possess an *ADH1B**2 allele (Goedde et al., 1992; Lee et al., 1997; Thomasson et al., 1991).

One mechanism by which it is hypothesized that these two genes give rise to lower rates of alcohol dependence is via increased levels of acetaldehyde, leading to more intense reactions to alcohol, decreased drinking and heavy drinking, and lower rates of alcohol-related problems (Thomasson et al., 1991). This mechanism is strongly supported for *ALDH2**2 but is less consistently supported for *ADH1B**2 (reviewed by Wall et al., 2005a).

Another important factor that has been associated with variability in response to alcohol and vulnerability for alcohol dependence is an individual's family history of alcoholism. A low level of response to alcohol is more common in both men and women with a first-degree family history of an AUD (Eng et al., 2005; Schuckit and Smith, 1996). This relationship has been found across ethnic groups, including Caucasians, Hispanics, and Native Americans (Ehlers et al., 1999; Schuckit et al., 1996, 2006). The prevalence of a family history of AUDs varies by ethnicity. In the United States, approximately 27% of Native Americans, 15% of the black and white populations, 14% of Hispanics, and 6% of Asian Americans reported "alcoholism" in a first-degree relative (Harford, 1992). These data are consistent with epidemiologic findings that Native Americans have the highest rates of AUDs and Asian Americans have the lowest rates, compared with other racial and ethnic groups in the United States (Grant et al., 2004; Zhang and Snowden, 1999).

Our laboratory assessed family history of alcohol dependence across Chinese- and Korean-American college students. Consistent with AUD epidemiologic data from Taiwan and South Korea (Helzer et al., 1990), we found that Korean Americans were significantly more likely to report a first-degree family history of alcohol dependence than Chinese Americans (17% vs 4%; Ebberhart et al., 2003). These results suggest that factors associated with a family history of alcohol dependence could be contributing to the different rates of AUDs found across these Asian subgroups. In addition, factors associated with a low response to alcohol, such as family history of alcoholism, as well as *ALDH2**2 and *ADH1B**2, may place individuals of Korean descent at increased risk for developing an AUD, compared with Chinese.

It also is possible that an individual's level of response to alcohol is influenced by environmental factors. For example, ethnicity and family history of alcoholism may contribute to differences in environmental contexts, such as exposure to parental modeling of alcohol behavior. Individuals with *ALDH2**2 and *ADH1B**2 alleles have at least one biological parent with these alleles and also may be exposed to lower levels of drinking. Prior research has demonstrated that parental modeling can affect the development of alcohol-related learning (e.g., expectancies; Brown et al., 1999; Sher et al., 1996), which could contribute to differences in conditioning aspects of alcohol sensitivity (Gabrielli et al., 1991).

The optimal method for measuring the level of response to alcohol is the alcohol challenge paradigm. This design provides the most objective information regarding variability in level of response to alcohol but is time consuming and costly to conduct. Additionally, participating in an alcohol challenge study might be unsafe for some individuals, such as pregnant women, those who are alcohol dependent, and Asians who are homozygous for the *ALDH2**2 allele. Individuals who are homozygous for *ALDH2**2 have been shown to have severe reactions to moderate doses of alcohol, including tachycardia, hypotension, nausea, and vomiting (Wall et al., 1992). Moreover, individuals with the most intense reactions to alcohol may not volunteer for alcohol challenge studies, resulting in participation bias (Heath et al., 1999).

The Self-Rating of the Effects of Alcohol (SRE) form was developed as an alternative to the alcohol challenge paradigm. The SRE is a 12-item questionnaire that asks DURANCEAUX ET AL. 229 participants to indicate the number of drinks required for them to feel up to four effects of alcohol. Higher scores on the SRE indicate that more drinks are required to have an effect, implying a lower level of response per drink. SRE values have correlated with data from alcohol challenge studies at about 0.4 to 0.6 (Schuckit et al., 1997a, 1997b) and have correlated with the *ALDH2**2 allele at 0.35 (Wall et al., 1999).

A prior study from our laboratory explored the SRE in a sample of Asian-American college students (Wall et al., 1999). The participants were of entirely Chinese ($n = 72$), Japanese ($n = 16$), or Korean ($n = 49$) descent who were genotyped for *ALDH2*. A low score on the SRE,

indicating a more intense response to alcohol, was associated with possession of an *ALDH2*2* allele. This association is consistent with the relationship between *ALDH2*2* and enhanced sensitivity to alcohol that has been found using alcohol challenge paradigms (Cook et al., 2005; Peng et al., 1999; Wall et al., 1992). The link between the SRE and *ALDH2* genotype remained significant after controlling for the effects of gender, body weight, and quantity and frequency of recent drinking (Wall et al., 1999). In addition, exploratory analyses were conducted to examine Asian subgroup differences related to a low level of response to alcohol, expressed as having a total SRE score of 4.5 or higher. A significantly greater proportion of Koreans (31%) had elevated SRE scores than Japanese (19%) or Chinese (8%). Ethnic subgroups, however, were not balanced with regard to gender, and, for this exploratory analysis, other variables were not controlled. The post hoc, exploratory nature of these analyses and the relatively small sample size necessitated replication in a larger sample, while taking into account the influence of potential confounding variables.

The current study was designed to address these limitations and to further examine the relationship between scores on the SRE in a new sample of Chinese- and Korean-American college students. We hypothesized that Koreans would have higher SRE scores (i.e., be low responders to alcohol), compared with Chinese, and that this relationship would remain significant after controlling for the effects of gender, body weight, recent drinking history, and *ALDH2* and *ADH1B* genotypes. We further hypothesized that the link between the SRE and ethnicity might be explained, in part, by differences in country of origin (born in the United States or foreign born) as a measure of sociocultural influence and/or first-degree family history of alcohol dependence.

Method

Procedure

The participants were 357 (49% female) college students between the ages of 21 and 26 years who self-reported that both biological parents were of entirely Chinese (46%) or Korean (54%) descent; 49% were born in the United States and 51% were foreign born. Participants were recruited by advertisements for a paid research project, and respondents were screened by telephone and scheduled for an in-person assessment. Written informed consent, approved by the University of California, San Diego, Human Research Protection Program, was obtained. A blood sample, collected from each subject by finger-tip puncture, was genotyped at the *ADH1B* single nucleotide polymorphism at amino acid 47 (rs1229984; Arg47His) and *ALDH2* single nucleotide polymorphism at amino acid 487 (rs671; Lys487Glu), using enzymatic amplification of genomic DNA followed by hybridization with allele-specific oligonucleotides (Crabb et al., 1989; Xu et al., 1988).

Each person was individually interviewed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), which includes demographic and individual characteristics (Bucholz et al., 1994, 1995). The Family History Assessment Module (FHAM; Rice et al., 1995) was administered to assess family history of alcohol dependence, based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994). An individual was defined as having a positive first-degree family history if either biological parent or a full sibling met DSM-IV criteria for alcohol dependence. The FHAM has been shown to have moderate agreement with direct interview data (Rice et al., 1995).

The Timeline Followback procedure (Sobell and Sobell, 1992) was used to assess alcohol use over the previous 90 days. Frequency was measured as the average number of drinking days, and quantity was measured as the average number of standard drinks per drinking occasion,

with a *standard drink* defined as 1–1.5 oz of 80 proof distilled spirits, 4 oz of wine, or 12 oz of beer.

The SRE was administered to provide a retrospective estimate of individual variation in the level of response to alcohol. This self-report questionnaire measures the number of standard drinks needed to experience up to four different alcohol effects: beginning to feel different (i.e., any effect); slurring speech or dizziness; loss of coordination or stumbling; and passing out or going to sleep when not wanting to. The SRE assesses these effects at three different time periods: the first five times one consumed alcohol, the most recent 3-month period of drinking, and the period of heaviest drinking. A respondent's total SRE score is calculated by summing the number of drinks reported in all endorsed cells and dividing by the number of cells endorsed. Lower levels of response to alcohol are indicated by higher overall scores on the SRE. Consistent with previous reports, *low responders* were defined as those who had a total SRE score of 4.5 or higher (Schuckit et al., 1997a, 1997b; Wall et al., 1999).

Data analysis

Participants were examined on demographics, *ALDH2* and *ADH1B* genotypes, and alcohol-related characteristics to evaluate potential differences between Chinese and Koreans, using *t* tests for continuous variables and chi-square for dichotomous variables. For bivariate correlations, four correlation coefficients were calculated. The Pearson product moment coefficient was used to examine the relationship between two continuous variables; the point-biserial correlation analyzed the relationship between continuous and dichotomous variables; the phi coefficient evaluated two dichotomous variables; and Spearman's rho was used for correlations involving ordinal variables. The primary analysis for this investigation explored the relationship of being a low responder to alcohol (i.e., $SRE \geq 4.5$) and all other measured variables. Multivariate regression analyses were conducted to evaluate the association of a low level of response to alcohol with first *ALDH2* and *ADH1B* genotypes, country of origin, and family history of alcohol dependence, with potential confounding variables (e.g., gender, height, weight, and quantity and frequency of recent drinking) entered into the model.

Results

Of the 357 individuals who participated in this study, 22 (68% female, 55% Korean) were lifetime abstainers or had no experience with any of the four types of effects on the SRE and thus were excluded from analyses. The final sample consisted of 335 individuals (48% female, 54% Korean) with a mean (SD) age of 21.7 (1.10) years.

Table 1 presents the means and standard deviations for continuous variables and the percentages for dichotomous variables for demographics, *ALDH2* and *ADH1B* genotypes, and alcohol-related characteristics according to Chinese and Korean ethnicity. Because of skewed distributions, the total SRE score, weight, and quantity and frequency of alcohol consumption were adjusted using log transformations to better approach a normal distribution, but raw scores are presented in Table 1. Koreans were significantly more likely to have a first-degree family history of alcohol dependence ($\chi^2 = 14.74$, 1 df, $p < .05$) and had a significantly higher drinking quantity ($t = 3.75$, 332 df, $p < .05$) and a higher total SRE score ($t = 5.52$, 333 df, $p < .05$) than Chinese. Chinese were significantly more likely to possess at least one *ALDH2**2 allele ($\chi^2 = 5.42$, 1 df, $p < .05$) than Koreans. Statistically significant differences in age ($t = 2.99$, $p < .05$) and weight ($t = -2.70$, $p < .05$) also were found, with Chinese being older and Koreans being heavier.

Bivariate correlations were calculated between all variables. Significant correlations (p values $< .05$) were found between low responders, total SRE score, and all other measured variables except for *ADH1B* genotype and country of origin.

Results of the logistic regression analysis are presented in Table 2. Variables were simultaneously evaluated in five blocks, with being a low responder the dependent variable. Parameter values are reported for this full model. Because previous research has demonstrated that gender, body size, and recent alcohol-use history influence response to alcohol (Schuckit and Smith, 1996; Schuckit et al., 1997b, 2005), five variables were entered into the first block of the model as controls: gender, height, weight, alcohol quantity, and alcohol frequency. This block was statistically significant ($\chi^2 = 115.17$, 5 df, $p < .05$). *ALDH2* and *ADH1B* genotype (as ordinal variables) were included in the second block ($\chi^2 = 14.73$, 2 df, $p < .05$), which also was statistically significant. The third block included country of origin and was not significant ($\chi^2 = 0.02$, 1 df, $p = .879$). The fourth block included family history of alcohol dependence, which was entered as a dichotomous variable, given that only three participants reported more than one alcohol-dependent first-degree relative; this block was not significant ($\chi^2 = 1.75$, 1 df, $p = .189$).

These results suggest that being born in the United States and having a first-degree family history of alcohol dependence were not related to being a low responder with the variables from blocks one and two entered in the model. Ethnicity was entered in the fifth block to allow assessment of the relationship between being a low responder and ethnicity after all other variables were considered. Ethnicity remained significantly related to level of response to alcohol ($\chi^2 = 8.21$, 1 df, $p < .05$), after taking into account the influence of the aforementioned variables. Korean Americans emerged as approximately 1.6 times more likely than Chinese to be low responders to alcohol.

To determine whether similar results would be found using the total SRE score measured as a continuous variable, a stepwise multiple regression analysis was conducted. The pattern of results from this analysis was consistent with that of the logistic-regression analysis. Ethnicity remained significantly related to total SRE score when gender, height, weight, alcohol quantity, alcohol frequency, *ALDH2*, *ADH1B*, country of origin, and first-degree history of alcohol dependence were included in the model ($F = 32.76$, 1/323 df, $p < .05$).

Discussion

The data reported here describe demographic, alcohol use, country of origin, family history of alcohol dependence, and *ALDH2* and *ADH1B* variables to better elucidate the relationship between scores on the SRE and ethnicity in Chinese- and Korean-American college students. As hypothesized and consistent with prior exploratory research (Wall et al., 1999), Koreans had higher average SRE scores and were more likely to be categorized as low responders, compared with Chinese. Importantly, the relationship between SRE and ethnicity remained significant, after a variety of factors were controlled for that could relate with level of response to alcohol, including gender, height, weight, recent alcohol consumption, *ALDH2* and *ADH1B* genotypes, country of origin, and family history of alcohol dependence. This result suggests that Koreans may have a lower level of response to alcohol, compared with Chinese, and that this relationship is not fully accounted for by these other variables.

As predicted, a first-degree family history of alcohol dependence was associated with a low level of response to alcohol as measured by the SRE, and Koreans were more likely than Chinese to report a first-degree family history of alcohol dependence. Contrary to our hypothesis, however, first-degree family history of alcohol dependence did not account for a significant amount of additional variance in SRE score, after the other covariates were controlled for. This finding implies that there are other factors associated with Korean ethnicity that contribute to the low level of response to alcohol in Koreans, relative to Chinese. It also is noteworthy that we did not find a significant relationship between first-degree family history

of alcohol dependence and *ALDH2* genotype, even though both of these variables have been shown to relate to level of response to alcohol and risk for alcohol dependence.

The lack of a significant relationship between *ADH1B* genotype and scores on the SRE also deserves comment. Although some studies have found that the *ADH1B**2 allele is associated with a lower rate of alcohol dependence (Tanaka et al., 1996; Wall et al., 2005b; Whitfield, 1997), others have not (Luczak et al., 2004; Takeshita et al., 1994). Furthermore, some alcohol challenge studies have found significant associations between *ADH1B* and level of response to alcohol (Cook et al., 2005; Duranceaux et al., 2006), but others have not (Heath et al., 1999; Peng et al., 2002). Thus, prior data do not consistently support the hypothesis that *ADH1B**2 leads to decreased rates of alcohol dependence via a more intense response to alcohol, and any such relationship may be further obscured when level of response to alcohol is assessed using self-report.

We also did not find a significant association between being born in the United States and SRE score. Country of origin is one indicator of an individual's level of acculturation and exposure to sociocultural influences, which potentially could have an impact on response to alcohol. A more detailed sociocultural measure might have resulted in different findings. The current study disaggregates two Asian- American subgroups that often are combined in epidemiologic research, but "Chinese" and "Korean" still represent broad classifications of individuals. More detailed specification of ethnic heritage (e.g., Han, Mongolian, Paiwan) as well as measuring additional sociocultural influences represents a needed area for future investigation. It also is possible that the relationships between variables influencing response to alcohol may be more complex (i.e., reciprocal and interactive) than can be tested by the cross-sectional data and additive models employed in the current study. A prospective study of these and other variables, ideally beginning before the onset of drinking, would allow for tests of mediation and provide a more complete understanding of causal relationships.

The results of this study also must be interpreted within the limits of the current methodology. With the exception of *ALDH2* and *ADH1B* genotypes, all data were obtained by participant self-report. Stronger relationships might have emerged with actual challenge data and direct family history data. Because all participants were college students, the external validity of these findings should be explored in other samples.

Although these limitations must be considered, the current investigation has important implications. This study underscores the need to disaggregate Asian subgroups when conducting alcohol-related research. The findings suggest that Koreans are more likely to experience a low level of response to alcohol, compared with Chinese, even with a variety of other factors controlled for. Additional studies should be conducted to elucidate other factors (e.g., unmeasured sociocultural and genetic factors) contributing to this response, as well as how they ultimately influence risk for developing an AUD. Insofar as much remains to be learned about the etiology of alcoholism in the general population, these findings will contribute to a greater understanding of racial and ethnic disparities in the causes and consequences of alcohol involvement and the generalizability of findings across groups.

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Table 1

Demographics, *ALDH2* and *ADH1B* genotypes, and alcohol-related characteristics according to ethnicity Chinese Korean

Variable	Chinese (<i>n</i> = 154)		Korean (<i>n</i> = 181)	
	Mean (SD)	Range	Mean (SD)	Range
Age, years *	21.9 (1.24)	21–26	21.6 (0.93)	21–26
Height, centimeters	167.8 (9.39)	147.3–190.5	169.6 (8.37)	150.0–190.5
Weight, kilograms *	62.4 (12.44)	36.4–109.1	65.8 (12.00)	43.2–102.3
Alcohol quantity, drinks per occasion previous 90 days *	2.3 (2.23)	0.0–17.0	3.4 (2.86)	0.0–16.3
Alcohol frequency, occasions over previous 90 days	9.4 (10.97)	0.0–65.0	12.1 (13.61)	0.0–80.0
Total SRE score *	3.2 (2.00)	0.3–12.2	4.6 (2.56)	0.8–15.1
	%		%	
Female		46.8		48.1
U.S. born		55.8		49.2
<i>ADH1B</i> genotype				
1/1		8.4		10.5
1/2		41.6		33.1
2/2		50.0		56.4
<i>ALDH2</i> genotype *				
1/1		53.3		65.7
1/2		38.3		30.4
2/2		8.4		3.9
First-degree family history of alcohol dependence *		1.3		12.2
Low responder, SRE $\geq$ 4.5 *		19.5		45.9

Notes: SRE = Self-Rating of the Effects of Alcohol.

* $p < .05$.

Table 2

Low response to alcohol and ethnicity: Influence of covariates, genotype, and family history of alcohol dependence on total SRE score of 4.5 or greater; full model parameter estimates (β), odds ratios (ORs), confidence intervals (CIs), and step chi-squares (χ^2) for total SRE score of 4.5 or greater

Step	Step χ^2 (p)	Variable	β (SE)	Wald χ^2	p	OR (95% CI)
1	115.17 (.000)	Gender	0.26 (.46)	0.31	.577	1.29 (0.53–3.16)
		Height	0.04 (.03)	2.12	.146	
		Weight	0.02 (2.90)	0.00	.996	
		Alcohol quantity	4.13 (.79)	27.29	.000	
		Alcohol frequency	1.16 (.42)	7.74	.005	
2	14.73 (.001)	ALDH2	–0.93 (.28)	10.78	.001	
		ADH1B	–0.23 (.22)	1.01	.314	
3	0.02 (.879)	U.S. born	0.03 (.27)	0.01	.922	1.03 (0.60–1.75)
4	1.75 (.186)	FH+ ^a	0.45 (.57)	0.60	.435	1.57 (0.51–4.83)
5	8.21 (.004)	Korean	0.45 (.16)	8.03	.005	1.57 (1.15–2.14)

Notes: Weight, alcohol quantity, and alcohol frequency scores were log-transformed to normalize the distributions for analyses. ORs and CIs are only reported for dichotomous variables. SRE = Self-Rating of the Effects of Alcohol;

^aFH+ = family history positive, that is, first-degree family history of alcohol dependence.