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A 5-Year Prospective Evaluation of DSM-IV Alcohol Dependence With and Without a Physiological Component

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Background: The DSM-III-R removed tolerance and withdrawal as required elements for a diagnosis of alcohol dependence. Although this practice was continued in DSM-IV, the more recent manual asked clinicians to note whether physiological aspects of withdrawal (tolerance and withdrawal) had ever been experienced. Few studies have determined the prognostic meaning of a history of a physiological component to DSM-IV alcohol dependence.

Methods: Face-to-face structured interviews were used to evaluate the course of alcohol, drug, and psychiatric problems during the subsequent 5 years for 1094 alcohol-dependent men and women. These subjects had been classified into subgroups at the time of initial interview regarding evidence of tolerance or withdrawal, and all evaluations were based on DSM-IV criteria. At baseline, the application of DSM-IV diagnostic guidelines resulted in 649 (59.3%) individuals having a history of an alcohol withdrawal syndrome, with or without tolerance (group 1); 391 (35.7%) with histories of tolerance but not withdrawal (group 2); and 54 (4.9%) with no lifetime histories of tolerance or withdrawal (group 3).

Results: During the 5-year follow-up, both the broad (group 1 plus 2 versus group 3) and narrow (group 1 versus group 2 plus group 3) definitions of physiological dependence were associated with more alcohol and drug problems. However, for most items, this differential primarily reflected differences between groups 1 and 3, with a less impressive effect by group 2. Although no group differences were noted for the rate of independent major depressive episodes, substance-induced depressions did differentiate among groups, a finding also most closely related to the distinction between groups 1 and 3.

Conclusions: These data support the prognostic importance of noting the presence of a physiological component in alcohol dependence and indicate the potential relevance of limiting the definition of a physiological component to withdrawal.

Key Words: Alcoholism, Tolerance, Withdrawal, Diagnosis.

THE DIAGNOSTIC CRITERIA for substance-use disorders (SUDs) continue to evolve (Babor, 1992; Bucholz, 1999; Caetano, 1987; Grant, 2000; Langenbucher et al., 1996; Schuckit et al., 1998b, 1999). When the DSM-III-R moved toward a broad definition of dependence, its authors deviated from the historical approach to SUDs that gave a special emphasis to the physiological aspects of tolerance and withdrawal (American Psychiatric Association, 1987; Langenbucher et al., 2000). There were several reasons for this change toward the approach of Edwards and Gross (1976), which emphasized the central salience that substances of abuse were occupying in an individual's life. These included the ability to apply dependence across a wider range of substances, several of which did not have clinically relevant withdrawal syndromes or levels of development of tolerance. This demotion from the central importance of tolerance and withdrawal, although it went against what had been used in most prior diagnostic schemes, was consistent with both the Feighner et al. (1972) approach and the Research Diagnostic Criteria (Spitzer et al., 1978).

However, there are some potential problems in viewing tolerance and withdrawal as equal in importance to other diagnostic items. First, the movement to the broad dependence syndrome was made without intensive study of the effect that would occur if neither tolerance nor withdrawal was required for a diagnosis. Second, the physiological aspects of this syndrome might be important in distinguishing between dependence and the second diagnostic cate-

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The Collaborative Study on the Genetics of Alcoholism (COGA) (H. Begleiter, State University of New York Health Science Center at Brooklyn, Principal Investigator; T. Reich, Washington University, Co-Principal Investigator) includes nine different centers where data collection, analysis, and/or storage takes place. The nine sites and principal investigators and co-investigators are the following: Indiana University (T.-K. Li, J. Nurnberger Jr, P. M. Conneally, and H. Edenberg); University of Iowa (R. Crowe and S. Kuperman); University of California at San Diego (M. Schuckit); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (B. Porjesz and H. Begleiter); Washington University in St. Louis (T. Reich, C. R. Cloninger, J. Rice, and A. Goate); Howard University (R. Taylor); Rutgers University (J. Tischfield); and Southwest Foundation (L. Almasy).

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gory, abuse, a label that also focuses on interference in behavior and daily functioning (Harford and Muthén, 2001; Muthén, 1996). Third, a history of withdrawal identifies individuals with potential special treatment needs, including those who might be particularly vulnerable toward relapse (Langenbucher et al., 2000; Schuckit et al., 1998b).

There is also debate regarding the best way to define a physiological component to dependence. Tolerance can be problematical in that it may be difficult to document from historical information (Langenbucher et al., 1997, 2000), and several studies suggest that withdrawal relates more closely to a history of severe clinical problems (Bucholz et al., 1996; Schuckit et al., 1998b, 1999).

A number of investigations have evaluated the cross-sectional and retrospective importance of tolerance, withdrawal, or both as indicators of a subtype of dependence. Several reported no clinical usefulness of a physiological dependence subdiagnosis, including data from a heterogeneous population of SUD patients in whom physiological symptoms did not relate to scores on the Addiction Severity Index (Carroll et al., 1994) and from two factor-analytic studies in the general population (Hasin et al., 1994; Muthén et al.,1993). Another evaluation of alcohol problems in cocaine-dependent subjects, however, reported a modest relationship between tolerance or withdrawal and the severity of alcohol problems as measured on the Addiction Severity Index (Rounsaville and Bryant, 1992). A more severe clinical course was also associated with withdrawal in a latent class analysis with more than 2500 relatives of alcohol-dependent probands (Bucholz et al., 1996), a factor analysis performed with 6000 current drinkers (Harford and Muthén, 2001), and an evaluation of 318 adult and 214 adolescent alcohol-dependent individuals (Langenbucher et al., 2000).

Our group published two cross-sectional and retrospective studies, including an evaluation of 3395 men and women with DSM-III-R alcohol dependence who were part of the Collaborative Study of the Genetics of Alcoholism (COGA; Schuckit et al., 1998b). Here, subjects with histories of either tolerance or withdrawal, especially the latter, had a higher maximum number of drinks per day, were more likely to report drinking while giving up obligations (i.e., binges), and had more additional alcohol-related life problems. The second evaluation, which involved more than 3000 individuals dependent on marijuana, cocaine, amphetamines, or opioids, also revealed that more intense problems were associated with histories of tolerance or, especially, withdrawal (Schuckit et al., 1999).

There are several 6- to 12-month follow-ups of SUD individuals with or without a physiological component. With one exception (a 6-month follow-up of 72% of a heterogeneous population of 521 mostly drug-dependent subjects; Carroll et al., 1994), the other studies reported that a history of withdrawal or tolerance was associated with a higher future rate of substance use or problems, although the intensity of the difference between subgroups was not apparent for all measures (Hasin et al., 2000; Langenbucher et al., 1997, 2000). The investigations included a 12-month follow-up component of a household survey of 130 alcohol-dependent subjects and a 6-month evaluation of 241 of 365 substance-dependent patients who received treatment. Our own group also evaluated the prognostic implications of the seven DSM-IV dependence items over 5 years in more than 600 alcohol-dependent individuals, for whom histories of withdrawal and, to a lesser extent, tolerance were among the most robust predictors of difficulties (Schuckit et al., 2002).

These analyses take advantage of 5-year follow-up data from the COGA sample to more directly evaluate the prognostic meaning of tolerance or withdrawal in a subset of subjects who had originally been assessed at baseline (Schuckit et al., 1998b). The analyses differ from prior reports in that subjects are now diagnosed with DSM-IV, rather than DSM-III-R, criteria, and a 5-year follow-up is used to evaluate the relationships of a history of a physiological dependence on alcohol to the course of alcohol, other substance-related problems, and psychiatric problems.

In summary, one prominent change from DSM-III-R to DSM-IV was the request to subtype dependence, and another was to raise the threshold for dependence from three of nine items to three of seven. The 5-year prognostic meaning of these changes has never been evaluated. We hypothesize that although both broad and narrow definitions of physiological dependence in DSM-IV will relate to a more problematic outcome, the greatest difficulties will be seen for alcoholics with a history of withdrawal.

METHODS

Data were generated after we obtained written, informed consent from participants among the original six centers of COGA (Bucholz et al., 1994; Schuckit et al., 1997, 1998b, 2001). The investigation began with an initial proband entering treatment for an alcohol-use disorder who met both the DSM-III-R definition (American Psychiatric Association, 1987) for alcohol dependence and the Feighner et al. (1972) criteria for definite alcoholism and who had multiple alcohol-dependent relatives available for study. Individuals with life-threatening illnesses were excluded, as were those with intense recent intravenous drug use and those who did not speak English.

All probands, as well as their first-degree relatives, were evaluated with the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA), a face-to-face instrument developed from a variety of existing diagnostic interviews (Bucholz et al., 1994; Hesselbrock et al., 1999; Spitzer et al., 1992). The validity of SSAGA alcohol-dependence diagnoses compared with another structured interview was 0.63, and the reliability for tolerance and withdrawal items was approximately 0.80, both across centers and across interviewers within a center (Bucholz et al., 1995; Hesselbrock et al., 1999). Trained interviewers gathered information relevant to 17 DSM-III-R and DSM-IV axis I diagnoses, as well as antisocial personality disorder, by using the timeline method described in more detail elsewhere to differentiate between psychiatric syndromes observed only in the context of a SUD (substance-induced conditions) and those that occurred independently of intoxication or withdrawal from a relevant substance (American Psychiatric Association, 1987, 1994; Schuckit et al., 1997). The same interview was used to assess all available relatives, as well as controls

Table 1. Baseline Demographic Characteristics of 1094 Alcohol-Dependent Subjects Divided Into Three Groups on the Basis of Baseline Lifetime Histories of Withdrawal, Tolerance (Without Withdrawal), or Neither

Variable	Group 1, withdrawal (n = 649; 59.3%)	Group 2, tolerance only (n = 391; 35.7%)	Group 3, neither (n = 54; 4.9%)	F(1,1091) or χ^2 (df = 1), groups 1 and 2 vs. 3	F(1,1091), or χ^2 (df = 1), groups 1 vs. 2 and 3	F(1,1091) or χ^2 (df = 1), group 1 vs. 3	F(1,1091) or χ^2 (df = 1), group 2 vs. 3	F(1,1091) or χ^2 (df = 1), group 1 vs. 2
Continuous (mean ± SD)								
Age (years)	37.7 ± 10.51	32.2 ± 10.03	36.8 ± 11.14	1.55	14.78***	0.45	9.34**	70.92***
Education (years)	12.7 ± 1.97	13.0 ± 1.98	12.9 ± 2.04	0.03	1.87			
Length of follow-up	5.4 ± 0.82	5.4 ± 0.96	5.3 ± 0.55	0.53	0.75			
Categorical (%)								
Male gender	67.3	61.9	50.0	5.24*	5.47*	6.68**	2.81	3.19
Race (3 *df*)				0.61	0.12			
Caucasian	76.1	76.2	74.1					
African American	14.2	14.1	16.7					
Hispanic	6.5	6.7	7.4					
Other	3.2	3.1	1.9					
Religious preference (3 *df*)				1.60	5.72			
Catholic	38.2	39.1	31.5					
Protestant, Fundamentalist, other Christian	45.0	38.9	50.0					
None/atheist	14.0	19.7	14.8					
Other	2.8	2.3	3.7					
Marital Status (3 *df*)				4.67	47.30***	4.75	8.23*	51.73***
Married	50.2	52.9	64.8		1.82		2.70	0.72
Widowed	1.5	1.0	0.0		0.86		0.56	0.49
Divorced or separated	34.4	17.7	24.1		33.33***		1.30	33.75***
Never married	13.9	28.4	11.1		26.56***		7.31**	33.00***
Currently employed full-time	40.1	55.8	55.6	1.90	26.06***	4.94**	0.00	24.19***
Proband status	61.0	24.0	27.8	7.72**	141.69***	22.68***	0.30	133.89***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

and their family members. The comparison subjects were identified by using a variety of methods across the six centers, including random selection from driver's license records, individuals attending dental and medical clinics, and university students.

A subset of original subjects and relatives was chosen for follow-up approximately 5 years after the initial interview. The group included probands, controls, their spouses and offspring, and additional individuals who had originally been genotyped (Preuss et al., 2002; Schuckit et al., 2002). The follow-up SSAGA was similar to the initial interview except for the greater detail for events occurring in the 5-year interval.

This report focuses on individuals who were followed up from among the initial 3395 men with alcohol dependence who were evaluated at baseline and divided into categories related to history of alcohol tolerance or withdrawal (Schuckit et al., 1998b). From these, 565 subjects were not appropriate for follow-up (e.g., were more distant relatives), and less than the required 5 years had passed for another 60. An additional 276 had died, and 932, although dependent in DSM-III-R, did not fulfill DSM-IV criteria for alcohol dependence, leaving 1562 men and women appropriate for these analyses. Follow-up data were obtained on 1094 (70.0%) of these, with the remainder fairly equally divided between subjects who could not be found and those who refused follow-up interviews.

The reinterviewed subjects were divided into groups relevant to their baseline lifetime histories of alcohol withdrawal, regardless of tolerance (group 1; 649 subjects; 59.3%); those who had reported tolerance but never experienced withdrawal (group 2; 391 subjects; 35.7%); and alcohol-dependent individuals without a history of either tolerance or withdrawal (group 3; 54 subjects; 4.9%). These groups were reformulated with DSM-IV criteria, and tolerance was operationalized to mean that the person endorsed needing 50% or more alcohol to produce a particular effect previously observed at a lower intake.

The statistical analyses first focused on the evaluation of individuals who met DSM-IV criteria for dependence with a physiological component, i.e., subjects in groups 1 and 2 versus group 3. We next determined how a more narrow definition of dependence functioned by comparing group 1 (with withdrawal) versus groups 2 and 3. If either of these two analyses revealed significant differences, a Tukey's most honestly significant post hoc analysis was used for continuous variables, and post hoc χ^2 tests were used for categorical data. Finally, backward-elimination logistical regression analyses were performed to evaluate the combination of outcome characteristics most closely tied to the baseline narrow (i.e., withdrawal only) or the broader (tolerance or withdrawal) definitions of physiological dependence.

RESULTS

At follow-up, the 1094 subjects were predominantly male (64.5%), had an average age of 41.1 years (SD, 10.74 years), and had an average of 5.4 years (SD, 0.87 years) of follow-up. Overall, these men and women had an average of 13.0 years (SD, 2.00 years) of education, 58.7% were employed full-time, and at the time of follow-up, 79.1% were married, 11.6% were widowed or separated/divorced, and 9.3% had never been married. Among these subjects, 46.2% were original probands, and the remaining individuals represented alcohol-dependent relatives of the original subjects or alcoholic individuals identified in the control families. The baseline demographic characteristics of this sample were similar to those of the 2242 alcohol-dependent subjects who were not followed up, except for a slightly greater number of years of education for this group (12.8 ± 1.90 vs. 12.6 ± 2.08; t = 2.91; 3334 df; $p < 0.01$).

The data across the tables evaluate how the groups established by baseline information differed during the follow-up interval. Table 1 demonstrates that both the broad (groups 1 and 2) and narrow (group 1) definitions of physiological dependence revealed no differential across groups on length of follow-up, education, race, or religion,

Table 2. Alcohol-Related Problems During Follow-Up for 1094 Alcohol-Dependent Subjects Divided Into Three Groups on the Basis of Baseline Diagnoses

Variable	Group 1, withdrawal (n = 649; 59.3%)	Group 2, tolerance only (n = 391; 35.7%)	Group 3, neither (n = 54; 4.9%)	F(1,1091) or χ^2 (df = 1), groups 1 and 2 vs. 3	F(1,1091), or χ^2 (df = 1), groups 1 vs. 2 and 3	F(1,1091) or χ^2 (df = 1), group 1 vs. 3	F(1,1091) or χ^2 (df = 1), group 2 vs. 3	F(1,1091) or χ^2 (df = 1), group 1 vs. 2
Continuous (mean ± SD)								
Number of 7 DSM-IV dependence criteria endorsed	2.7 ± 2.64	1.7 ± 1.86	1.4 ± 1.70	5.06*	31.98***	13.52***	0.55	41.55***
Number of 4 DSM-IV abuse criteria endorsed	1.6 ± 1.55	1.3 ± 1.37	1.0 ± 1.26	4.32*	11.53***	7.22**	1.91	7.91**
Number of 15 additional problems endorsed	5.1 ± 4.06	2.9 ± 3.18	1.9 ± 2.57	17.05***	79.89***	38.30***	3.66	87.44***
Maximum number of drinks in the last 6 months for drinkers (n = 642)	13.9 ± 11.89	10.8 ± 8.96	7.7 ± 5.80	8.07**	20.47***	13.57***	3.32	13.43***
Categorical (%)								
Abstinent for all of follow-up	31.5	18.4	7.4	9.79**	28.02***	13.67***	4.06*	20.76***
DSM-IV dependence items								
Tolerance	43.5	40.4	27.8	4.46*	2.28	5.02*	3.19	0.93
Withdrawal syndrome	35.4	10.7	7.4	9.56**	88.18***	17.64***	0.57	77.06***
Larger amount, longer than intended	52.5	54.7	51.9	0.05	0.36			
Persistent desire to cut down or control use	32.7	14.1	18.5	1.39	45.53***	4.62*	0.75	44.23***
Great deal of time obtaining, using, or recovering from effects	30.4	14.1	13.0	3.61	39.40***	7.32**	0.05	35.26***
Important activities given up or reduced	38.2	18.2	14.8	6.16*	52.73***	11.79***	0.36	46.15***
Continued use despite physical or psychological problems	34.1	17.7	11.1	7.32**	39.57***	12.00***	1.45	32.66***
DSM-IV abuse items								
Interference with major role	41.5	24.3	25.9	1.87	33.56***	4.99*	0.07	31.55***
Use in hazardous situations	49.9	50.1	40.7	1.76	0.09			
Legal problems	19.0	14.6	5.6	5.09*	5.67*	6.08*	3.31	3.26
Use despite social problems	49.5	44.3	31.5	5.29*	4.85*	6.46*	3.16	2.66
Other alcohol-related problems								
Intoxication for ≥2 days (binge)	38.4	17.9	13.0	7.70**	55.99***	13.89***	0.81	48.05***
Blackouts	46.1	37.6	31.5	2.74	9.19**	4.29*	0.76	7.16**
Early morning drinking	45.8	25.1	13.0	13.82***	55.81***	21.85***	3.85*	44.38***
Compelling desire to drink	36.2	14.8	5.6	13.31***	67.73***	20.92***	3.45	55.10***
Mixing drugs and alcohol known to be dangerous	29.0	20.7	7.4	9.34**	13.73***	11.67***	5.44*	8.66**
Nondriving alcohol arrests	13.7	9.7	3.7	3.57	5.67*	4.43	2.10	3.63
DUI	14.6	12.8	3.7	4.63*	1.98	5.01*	3.79	0.70
Driving accident while drinking	13.6	11.0	9.3	0.53	1.86			
Fights while drinking	57.2	49.4	35.2	7.48*	9.62***	9.75**	3.82	5.99*
Injury while drinking	21.6	17.4	5.6	6.88**	5.35*	7.89**	4.96*	2.67
Psychological impairment	39.3	16.4	9.3	11.29***	71.65***	19.29***	1.83	60.29***
Shakes after abstinence (not full withdrawal)	25.6	2.8	1.9	8.67**	101.45***	15.49***	0.17	89.53***
DTs/hallucinations after abstinence	10.0	1.5	0.0	3.94*	32.68***	5.96*	0.84	27.59***
Ever mention problem with drinking to a professional	58.2	26.9	25.9	8.72**	105.67***	21.11***	0.02	96.65***
Ever in treatment	64.4	27.9	24.1	14.53***	144.52***	14.53***	0.35	130.26***

DUI, driving under the influence; DTs, delirium tremens.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

whereas overall differences across groups were noted for age, gender, marital status, employment, and the proportion of probands. Post hoc analyses revealed that subjects with histories of withdrawal differed from those with tolerance (group 1 vs. 2) by being older, more likely to be separated or divorced, less often employed, and more often probands. Group 3 subjects, with histories of neither tolerance nor withdrawal, were different from those in group 2; they were older, and a lower proportion was single, although fewer demographic differences were seen for group 3 versus group 1.

Regarding the subsequent 5-year course of alcohol-related problems, as shown in Table 2, those with either the broad or narrow definition of physiological dependence

Table 3. Illicit Drug Use and Depressive Episodes During Follow-Up for 1094 Alcohol-Dependent Subjects Divided Into Three Groups on the Basis of Baseline Diagnoses

Variable	Group 1, withdrawal (n = 649; 59.3%)	Group 2, tolerance only (n = 391; 35.7%)	Group 3, neither (n = 54; 4.9%)	F(1,1091) or χ^2 (df = 1), groups 1 and 2 vs. 3	F(1,1091), or χ^2 (df = 1), groups 1 vs. 2 and 3	F(1,1091) or χ^2 (df = 1), group 1 vs. 3	F(1,1091) or χ^2 (df = 1), group 2 vs. 3	F(1,1091) or χ^2 (df = 1), group 1 vs. 2
Continuous (mean ± SD)								
No. Illicit drugs used	1.0 ± 1.31	1.0 ± 1.32	0.5 ± 1.00	5.93*	2.72	5.03*	6.27*	0.51
No. Illicit drugs dependent on	0.4 ± 0.80	0.3 ± 0.65	0.1 ± 0.44	6.51*	10.57**	8.65**	4.17*	3.51
Categorical (%)								
Drugs used								
Cannabinol	34.4	41.7	24.1	3.77	3.07			
Amphetamines	9.6	10.0	1.9	3.75	0.10			
Cocaine	23.6	26.9	14.8	2.79	0.47			
Sedative/hypnotics	11.3	9.0	5.6	1.31	2.13			
Opioids	16.2	12.8	5.6	3.63	3.89*	4.33*	2.37	2.21
Drugs dependent on								
Cannabinol	13.7	12.3	5.6	2.67	1.20			
Amphetamines	5.1	4.1	0.0	2.66	1.37			
Cocaine	15.3	14.3	7.4	2.32	0.67			
Sedative/hypnotics	2.9	0.5	0.0	1.11	8.61**	1.63	0.28	7.20**
Opioids	6.6	3.6	0.0	3.12	6.47*	3.81	2.00	4.37*
Depression								
Any depressive episode	29.4	16.4	9.3	6.60**	28.25***	10.09***	1.83	22.49***
Independent depressive episode	12.8	9.7	5.6	1.89	3.26			
Induced depressive episode	16.6	6.7	3.7	3.98*	25.97***	6.32*	0.70	21.70***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

reported more alcohol-related problems and a higher maximum number of drinks per occasion. Regarding specific groups, significantly higher values were generally seen for group 1 (withdrawal) compared with group 2 (tolerance alone) and for group 1 versus group 3 (neither tolerance or withdrawal), whereas groups 2 and 3 were not significantly different. The main exception to this pattern was the higher rate of continuous abstinence for the follow-up period for subjects in group 1. This differential remained when only nonprobands or when the 431 subjects who had never received formal inpatient or outpatient treatment at baseline evaluation were considered separately.

Table 3 offers information about the pattern of use and problems associated with illicit substances during the 5-year follow-up, as well as the self-report of DSM-IV substance-induced and -independent mood disorders. Both definitions of physiological dependence were associated with more drug dependencies, especially on opioids, mostly reflecting the higher rates for group 1 subjects. Men and women with histories of withdrawal were also more likely to experience substance-induced, but not -independent, depressive episodes during the 5 years.

Because Table 1 revealed some demographic differences across groups, the data were reanalyzed for the 589 nonprobands, of whom 43.0% were in group 1, 50.4% in group 2, and 6.6% in group 3. The pattern of differences across groups demonstrated in the tables remained for this nonproband subsample, including the differential across groups on the proportion with abstinence. Similarly, separate analyses were performed for the 706 men (61.9% in group 1, 34.3% in group 2, and 3.8% in group 3), with results again supporting the general pattern of findings noted in the tables. The same generic conclusion applies to the 388 women (54.6% in group 1, 38.4% in group 2, and 7.0% in group 3). The relationships among groups were also reanalyzed for the 642 alcoholics who reported drinking during the 6 months before the follow-up interview, including 317 (49.4%) in group 1, 282 (43.9%) in group 2, and 43 (6.7%) in group 3. The patterns across groups in Tables 2 and 3 generally remained for this subsample. One consistent difference was higher quantities of alcohol consumed and more alcohol-related problems for individuals in Groups 1 and 2, with a subsequent greater number of items on post hoc analyses that were significantly different between individuals in group 2 and group 3. A second consequence of the focus on drinkers is that DSM-IV dependence item 3 (drinking in larger amounts or longer than intended) was now modestly different across the groups, as was abuse item 2 (use in hazardous situations).

The data in Tables 1 through 3 do not indicate how items related to demography or the clinical course over the subsequent 5 years performed when considered together. Two approaches were used to address this question. First, the logistical regression analyses in Table 4 were performed to offer data more directly relevant to clinical settings. The first of these used relevant items from Tables 1 through 3 that were significantly different for the broad definition of physiological dependence as established at baseline (i.e., groups 1 and 2 vs. 3), and the second regression analysis focused on those demographic and outcome characteristics that were significantly different for the narrow definition of physiological dependence (i.e., group 1 vs. 2 and 3) as established at baseline. The specific items entered were selected to avoid obvious multicollinearity, where, for example, reflecting the high correlations between the number of dependence criteria endorsed and the maximum number

Table 4. Backward-Elimination Logistical Regression Analyses Predicting Withdrawal and Tolerance or Withdrawal Only Among 1094 Alcohol-Dependent Subjects

	Baseline dependent variables					
	Broad definition, withdrawal or tolerance (groups 1 and 2)			Narrow definition, withdrawal (group 1)		
Demographic and follow-up characteristics	Standardized estimate	Wald χ^2	Odds ratio	Standardized estimate	Wald χ^2	Odds ratio
Baseline demographics						
Age	NA			0.26	35.72***	1.04
Male gender						
Separated or divorced	NA					
Full-time employed	NA			−0.08	4.42*	0.74
Proband status				0.24	26.29***	2.40
Follow-up experiences for alcohol						
Number of dependence items endorsed	0.35	11.07***	1.30	0.27	25.19***	1.22
Abstinent for all of follow-up	0.53	17.00***	9.24	0.27	33.44***	3.03
Ever in treatment				0.19	14.27***	1.97
Follow-up experiences for drugs and depression						
Number of drug dependencies during follow-up	0.34	5.44*	2.30			
Induced depressive episode during follow-up				0.12	6.84**	1.93
Variance accounted for		11.1% (df = 3)			32.4% (df = 7)	

All variables listed were entered into the relevant logistical regressions, except for those labeled NA, which, reflecting results in earlier tables, were entered into one but not the other regression. Standardized estimates are given only for those variables that remained in the backward logistical regression.

* Wald statistics significant at $p < 0.05$; ** Wald statistics significant at $p < 0.01$; *** Wald statistics significant at $p < 0.001$.

of drinks and the number of abuse or other alcohol problem–related items, only one (the number of dependence items) was used in the regression. Similarly, among the 15 alcohol-related problems, 1 was selected as potentially salient (ever being in treatment during follow-up), and the group differential throughout the 5 years on the proportion who were abstinent was also entered. One item was selected as representative of the drug-related history during the 5 years of follow-up, and one related to depressive episodes. For the broad definition of dependence, only three items remained in the regression, accounting for 11% (the pseudo R^2) of the variance. These included the number of alcohol-dependence items endorsed during follow-up, the proportion who were abstinent during the entire follow-up period, and the number of dependencies on illicit drugs observed during follow-up. The regression analysis regarding the more narrow definition of withdrawal as established at baseline incorporated seven items, which combined to explain 32.4% of the variance. These included three demographic characteristics (age, employment status, and being a proband) as established at baseline. Four outcome items continued to relate to the narrow definition of withdrawal, even when considered in the context of demography. These included the number of alcohol-dependence items endorsed during follow-up, the proportion of subjects who were abstinent throughout the 5 years, the proportion who entered treatment during follow-up, and the experience of substance-induced depressive episodes during the follow-up period.

The variables in Table 4 were also entered into the more statistically efficient multinomial logistical regression looking across the three groups in Tables 1 to 3. This approach considers both broad and narrow definitions at the same time, but it does not show which items relate to which definition of physiological dependence. Almost all the same items as seen in Table 4 contributed significantly to the regression, except for the number of drug dependencies during follow-up, which was replaced by age (Wald χ^2, 19.26; standard estimate, 0.11; odds ratio, 1.03). In the multinomial regression, 30.0% of the variance was accounted for.

DISCUSSION

The data presented here describe the largest and longest prospective evaluation of the clinical course associated with the DSM-IV designation of alcohol dependence with a physiological component. Consistent with most of the relevant cross-sectional and prior shorter prospective studies, the data revealed a more severe clinical course of SUDs for those with a physiological component to their alcohol dependence at baseline (Bucholz et al., 1996; Harford and Muthén, 2001; Hasin et al., 2000; Langenbucher et al., 2000; Rounsaville and Bryant, 1992). Similar to our prior retrospective analyses (Schuckit et al., 1998b), a physiological component was associated with a higher number of maximum drinks and an increased number of alcohol-related life problems. Neither the current nor the prior study indicated that physiological dependence was related to independent depressions, although, perhaps reflecting the greater intensity of the alcohol-related problems, it was related to substance-induced mood disorders (Schuckit et al., 1997, 1998b). The more severe clinical course for subjects with a physiological component remained robust when gender and initial proband status were entered into the logistical regression analyses and when relevant subgroups (e.g., nonprobands, males or females, and current drinkers) were each evaluated separately.

Most of the effect of a physiological component to dependence on the subsequent course of alcoholism was explained by withdrawal. Most alcohol problems during follow-up were more intense for subjects who had reported

histories of withdrawal at baseline, and more of the variance related to the outcome in Table 4 was explained for the narrow (withdrawal only) versus the broad definition of a physiological component. These results are consistent with the relatively robust performance of withdrawal compared with other DSM criterion items in a prior analysis (Schuckit et al., 2002) and with most of the studies comparing withdrawal and tolerance in the literature (Bucholz et al., 1996; Harford and Muthén, 2001; Langenbucher et al., 2000; Schuckit et al., 1998b).

Several hypotheses have been put forth regarding the reasons why withdrawal might perform in a more robust manner than tolerance. First, the notation of an abstinence syndrome is based on relatively distinct physiological symptoms that might be easier for subjects to accurately remember and report, whereas tolerance requires a more cumbersome determination of changes in the number of drinks required for various effects (Langenbucher et al., 2000; Martin and Moss, 1993). Second, the need for more drinks to have an effect than had historically been true (i.e., tolerance) is likely to be observed, at least in a mild form, fairly early in SUDs and is also likely to be reported by people who do not fulfill criteria for dependence (Schuckit et al., 1995, 1998a). In any event, these data, along with most of the relevant prior studies, indicate that the DSM-V should consider requiring a subtyping of alcohol-dependent individuals into those with and without a physiological component but should base the criteria on a history of withdrawal.

One outcome characteristic requires more comment. Although a physiological component to alcohol dependence, especially if it included withdrawal, was consistently associated with a worse clinical outcome, the rate of abstinence over the 5 years of follow-up was highest for those individuals with histories of withdrawal at baseline. This finding remained even when subjects who were in treatment at intake into the study (i.e., probands) were excluded or when only subjects who had never received formal inpatient or outpatient treatment were analyzed. There is some indication from the literature that a greater severity of problems at initial evaluation in alcoholics (e.g., a history of withdrawal) might be associated with a higher probability of abstinence at follow-up (Curran and Booth, 1999). However, most studies demonstrate a more problematic outcome for those reporting greater levels of problems at baseline (Mattson et al., 1998; Powell et al., 1998). The reasons for these differences across investigations will have to be evaluated in additional studies, perhaps by more closely controlling for levels of motivation, the effect of concomitant medical problems, and additional treatment opportunities that might be offered those with histories of withdrawal. These elements might enhance the rate of abstinence overall, but not affect the pattern of drinking if a person returns to the use of alcohol. Regarding this study, it is important to note that even though subjects in group 1 reported higher rates of abstinence, the group as a whole demonstrated more severe alcohol-related problems.

These results must be interpreted in light of the methods used. First, only a subgroup of the original subjects was followed up, and 30% of these were not yet interviewed. However, there were no clinically relevant differences in demography between those subjects with DSM-IV alcohol dependence who were evaluated at baseline and those who were successfully followed up. Second, the original COGA subjects, or probands, were selected in a manner that emphasized both the severity of their alcohol dependence (i.e., they entered treatment) and the higher density of alcohol-use disorders in their families. However, our results held even if nonprobands were evaluated. Third, in contrast to a prior cross-sectional analysis that looked across a variety of drugs of abuse (Schuckit et al., 1999), this prospective study gathered information only from individuals who had met the criteria for alcohol dependence at baseline, and the prognostic meaning of a physiological component for dependence on other drugs must be evaluated further. Finally, all outcomes evaluated here came from self-reports, without corroborating data. However, the major conclusions, including the clinical relevance of a distinction between alcohol dependence with and without a physiological component and the preeminent position occupied by withdrawal, are consistent with much of the literature. These data underscore the need for the work group addressing DSM-V to consider requiring clinicians to subtype at least alcohol dependence by using a history of withdrawal as the criterion for a physiological component.

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