Withdrawal and Tolerance: Prognostic Significance in DSM-IV Alcohol Dependence*

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ABSTRACT. *Objective:* The clinical and research importance of tolerance and/or withdrawal in the diagnosis of substance dependence has been identified as a key area needing clarification. Earlier longitudinal studies did not identify whether diagnoses of alcohol dependence were current or lifetime. In this study, the prognostic significance of the DSM-IV physiological specifier was investigated among cases of alcohol dependence current at the baseline interview. The role of tremors, required in DSM-III and DSM-III-R, was investigated as well. *Method:* Household residents {*N* = 130; 57% men) meeting full criteria for current DSM-IV alcohol dependence in a baseline interview were re-interviewed a year later and DSM-IV alcohol dependence was again evaluated. Reliable structured interviews were used to make the diagnoses. The DSM-IV physiologic specifier and its components were tested as predictors of outcome of DSM-IV alcohol dependence, and included an additional definition of alcohol withdrawal that required tremors. Chi-square tests and adjusted odds ratios indicated statistical significance of group differences on outcome. *Results:* The DSM-FV physiological specifier (tolerance or withdrawal) did not predict 1-year chronicity of DSM-IV alcohol dependence, nor did tolerance when considered separately. However, withdrawal predicted poor outcome (e.g., 1-year chronicity of DSM-IV alcohol dependence). The effect of withdrawal was strengthened when tremors were required as part of the withdrawal syndrome. *Conclusions:* In contrast to earlier longitudinal research, this study supports the prognostic relevance of one component of the present DSM-IV physiological specifier—withdrawal. Withdrawal appears to have stronger prognostic meaning when the DSM-III-R version, in which tremors were required, is used. Further studies of the physiological subtype may benefit from studying subjects who have been clearly identified at the baseline evaluation as having a current diagnosis of dependence. *(J. Stud. Alcohol* 61: 431-438, 2000)

THE CLINICAL AND RESEARCH importance of alcohol withdrawal and tolerance in the diagnosis of alcohol dependence has been unclear for many years. Although the Feighner criteria (Feighner et al., 1972) and the Research Diagnostic Criteria (Spitzer et al., 1978) differed considerably in structure, both allowed alcoholism to be diagnosed without withdrawal or tolerance. In contrast, DSM-III required evidence of tolerance and/or withdrawal as the key element differentiating alcohol dependence from abuse. In DSM-III-R, DSM-IV and ICD-10, withdrawal and tolerance were once again among the dependence criteria but were not required to make a diagnosis. Note that DSM-III and DSM-III-R both required tremors for alcohol withdrawal to be diagnosed, but not DSM-IV. This change received little attention, but potentially changes the nature of the alcohol withdrawal syndrome.

The role of tolerance and withdrawal was the first issue faced by the DSM-IV work group on substance use disorders (Cottler et al., 1995). In a 1992 National Institute on Drug Abuse technical review group, concerns were raised about the measurement problems of tolerance, and the fact that tolerance is not generally a focus of treatment while a clinically severe level of withdrawal often is. The group recommended that if a physiological subtype of dependence was included in DSM-IV, it should be for a withdrawal syndrome only (Hasin et al., 1995).

A number of published studies on the definitions of alcohol withdrawal and tolerance and their role in alcohol dependence have been conducted with the Comprehensive International Diagnostic Interview (CIDI; Cottler et al., 1989, 1991). The CIDI provides lifetime diagnoses of substance use disorders, as well as information on symptom onset. These features offer benefits for studies on a variety of research questions. However, features of the CIDI preclude investigation of certain research questions. For example, the CIDI does not determine whether dependence symptoms co-occurred (as required in DSM-IV). Further, the CIDI does not indicate whether or not dependence is current at the time of the interview. In samples of mixed drug and alcohol patients, this feature of the CIDI precludes cross-sectional research on subsets of cases identified as having current diagnoses of alcohol dependence. It also precludes prospective research on remission of alcohol dependence among subjects identified with the disorder at a baseline interview. Another characteristic relevant to the physiological subtype is the CIDI handling of withdrawal in DSM-III-R. The CIDI

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algorithm for DSM-III-R alcohol withdrawal omitted the requirement for tremors. Thus, any comparison of DSM-III-R and DSM-IV alcohol withdrawal with CIDI data would not reflect this change in diagnostic criteria.

In the DSM-IV field trials. Cottler and colleagues (1995) used cross-sectional tabulations to investigate the roles of tolerance and withdrawal and "the prominence that should be given to these two symptoms." They reported that between 86% and 99% of subjects meeting criteria for dependence on alcohol or drugs reported tolerance, withdrawal or both. Although Cottler et al. (1995) stated that "these data alone [presumably the frequencies] are not sufficient to determine any special relevance of these physiological dependence symptoms," no further discussion or tests were presented. The DSM-IV work group then opted for a set of criteria with an additional modifier, "with or without physiologic dependence." More recently, the head of the DSM-IV work group again suggested that a key question concerning DSM-V dependence was the position of tolerance and/or withdrawal (Schuckit, 1996). This question appeared to reflect the feeling that the issue remained unresolved.

Research relevant to the DSM-IV physiological specifier since the field trials included several studies of different types. In 1988, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsored a supplement to the National Health Interview Survey (Grant et al., 1992) that included a detailed measure of current (last 12 months) alcohol dependence. Cross-sectional psychometric work conducted with these data (Muthén, 1996) showed that no criteria for alcohol dependence appeared to warrant greater than unit weighting, and that tolerance and withdrawal were not among the best indicators of alcohol dependence. Two clinical studies investigated predictive validity. However, rather than remission of DSM-IV alcohol dependence, a variety of other outcome measures were employed as validators. In a mixed sample of drug, psychiatric and alcohol patients and individuals selected from a local telephone book, Carroll et al. (1994) found little predictive utility in components of the alcohol physiological specifier in predicting 6-month follow-up ASI composite scores for alcohol or other types of physiological dependence. The relevance of the ASI composite scores to subjects who were not alcohol dependent at baseline is not clear. Because the CIDI was used, information on whether subjects were dependent on alcohol at baseline was not available. Langenbucher and colleagues (1997) used the CIDI to study substance abuse patients who were drinkers. They showed that the DSM-IV physiological specifier did not predict shorter time from the baseline interview to first drink. The use of a 25-item dependence scale showed stronger relationships to some but not all outcome measures used. Again, the specific relevance of the outcome measures to alcohol dependence was unclear, since an unknown number of the subjects did not have alcohol dependence at baseline. These studies suggest a lack of clinical relevance for the physiological specifier for DSM-IV alcohol dependence, but the methodological shortcomings make interpretation difficult.

The results of cross-sectional research conducted by Schuckit and colleagues (1998) contrasts with the longitudinal results. In a large study they found support for the clinical relevance of the physiological subtype of alcohol dependence, especially the withdrawal component. In this study, DSM-III-R diagnoses for alcohol dependence and alcohol withdrawal were used, including the DSM-III-R requirement for tremors in alcohol withdrawal. The study used cross-sectional data to show that the DSM-III-R physiological subtype of alcohol dependence appeared to be an important clinical indicator since subjects with the subtype were more likely to have many other indicators of severe alcohol dependence. However, the relevance of these results to the DSM-IV physiological specifier for alcohol dependence is uncertain, as the DSM-III-R definition of alcohol withdrawal included the requirement for tremors subsequently removed in DSM-IV. Support was also found for the clinical relevance of the physiological specifier for marijuana, cocaine, stimulants and opioids, especially withdrawal (Schuckit et al., 1999).

Sources indicate that, in patient samples, the prevalence of tremors as a component of alcohol withdrawal is between 25% and 30%. These include-results of a study of over 1,000 patients conducted several years ago (Whitfield et al., 1978) as well as data from a more recent clinical sample of 296 patients (Hasin et al., 1997a). Test-retest data from the 296 alcohol and drug patients (Hasin et al., 1997a) showed that the reliability of alcoholic tremors *(k* - .74) was significantly better than the reliability of the other alcohol withdrawal symptoms (range, .53 - .61) listed in DSM-IV. Thus, the decision to retain or drop tremors in the definition of alcohol withdrawal has the potential to change the apparent prevalence of withdrawal as well as change the validity and/or severity of the condition that is measured.

The nature of the work on the physiological subtype and the contradictions between the cross-sectional and longitudinal findings raised a number of questions. First, would results obtained from studies on longitudinal course provide more support for the physiological subtype in a sample of subjects who were all clearly identified as meeting full criteria for DSM-IV alcohol dependence at baseline? Studying time from a baseline interview to first drink as an indicator of relapse among individuals who do not have alcohol dependence in the first place is not an informative method to study the importance of the physiological specifier to alcohol dependence or other features of alcohol withdrawal.

Second, would results on longitudinal course be different in prospective longitudinal research in a community sample of individuals meeting current criteria for DSM-IV alcohol dependence at a baseline interview? The use of such a sample would preclude the effects of selection bias (Cohen and Cohen, 1984). In a sample of individuals who were all or

almost all untreated, such a sample would more fully reflect the natural history of the disorder.

Third, would results on longitudinal course support the physiological subtype more strongly if the outcome were defined in terms of the disorder of interest (specifically, remission or chronicity of alcohol dependence) rather than some other outcome? This question is important if one is interested in knowing about the specificity of an effect to alcohol dependence, rather than to a related but different area such as medical comorbidity or psychosocial disability.

Fourth, would results on longitudinal course provide stronger support for the physiological subtype if the older definition of withdrawal, requiring tremors, were used? This criterion was dropped from DSM-IV without published explanation. The cross-sectional work of Schuckit and colleagues (1998), showing the importance of the physiological specifier, used DSM-III-R criteria. No studies known to us have systematically investigated whether the requirement for tremors in the definition of alcohol withdrawal DSM-IV produces differences in predictive utility.

To answer these questions, we studied the influence of various aspects of the physiological specifier on the 1-year course of DSM-IV alcohol dependence in a sample of household residents who all met full criteria for current DSM-IV alcohol dependence at baseline. Our outcome was remission/chronicity of DSM-IV alcohol dependence at the follow-up interview. We tested both the old and new methods of defining alcohol withdrawal.

Method

Subjects for this study were part of a larger study of household residents in a sociodemographically diverse area near New York City. The methods of the full study have been presented elsewhere (Hasin et al., 1996, 1997b). In brief, households were designated via random digit dialing. Randomly designated members of each household were screened for eligibility for the study. Eligibility criteria included: drinking five or more drinks at least once in the year prior to screening, being within the ages of 18 and 65, and speaking English. Of those screened and eligible, 92% participated. Of these, 90% (n = 876) participated in a second interview, approximately a year later (mean time between interviews, 13.6 months), that provided the follow-up diagnostic data. After complete description of the study to the subjects, written informed consent was obtained. There were no statistically significant differences between those followed up and those not followed in terms of age, gender, race, average ethanol consumption at baseline, proportion of subjects with current alcohol dependence or abuse at baseline, or with individual symptoms of current alcohol dependence or abuse at baseline. This report focuses on the subjects who met full criteria for current DSM-IV alcohol dependence at the time of their baseline interview who were followed up 1 year later (130 out of 145 subjects, or 90%).

In this subsample (N = 130, 57% men) the mean (±SD) age was 31.0 ± 9.6 years. Mean years of education was 13.4 ± 2.3. Minority residents constituted about 21.5% of the sample, consistent with the underlying population of the area.

The Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS; Grant et al., 1995) was used to assess the symptoms and criteria of alcohol use disorders. The AUDADIS is a fully-structured interview designed to be used by lay interviewers in a large NIAAA-sponsored U.S. national survey (Grant, 1992). This instrument has been used in over 40 publications on aspects of DSM-IV alcohol dependence in the U.S. general population (e.g., Chou et al., 1996; Dawson 1996; Grant 1996, 1997; Grant and Dawson, 1996, 1997) as well as in international research (Üstün et al., 1997). The instrument itself has been presented in detail elsewhere (Canino et al., 1999; Chatterji et al., 1997; Grant et al., 1995; Hasin et al., 1996).

Consistent with the DSM-IV, AUDADIS diagnoses of alcohol dependence require that at least three dependence symptoms cluster together in time, representing a syndrome. Computer algorithms operationalize the diagnostic criteria from the numerous items on the dependence criteria in the interview. In contrast to other diagnostic instruments designed for survey interviewers, the AUDADIS is advantageous for studies involving questions on alcohol withdrawal because withdrawal symptoms are coded separately. The AUDADIS includes symptoms such as autonomic hyperactivity, tremors, insomnia, nausea or vomiting, transient hallucinations or illusions, psychomotor agitation, anxiety and seizures. The AUDADIS also includes headaches in the list of symptoms of withdrawal, in order to assess DSM-III definitions of withdrawal. However, in this study these were not included in the algorithm for DSM-IV withdrawal. In order to be inclusive, respondents are asked if these symptoms occurred when the effects of alcohol were wearing off, several hours after drinking, or the morning after drinking. Current AUDADIS DSM-IV alcohol dependence diagnoses have shown excellent test-retest reliability in several studies, including: a study of 473 household residents (k = .82; Grant et al., 1995); 50 patients in the parent study from which this report emerges {k = .81; Hasin et al., 1996); and a study of 296 patients in psychiatric and substance abuse treatment (k = .76; Hasin et al., 1997a). We created the variable representing withdrawal with tremors from the withdrawal items by requiring tremors in addition to at least one other alcohol withdrawal symptom.

The follow-up AUDADIS interview was developed for the present study. The alcohol diagnostic sections were exactly like the AUDADIS described above except that the timeframe covered only the period between baseline and follow-up. We tested outcome using DSM-IV definitions of both partial and full remission from DSM-IV alcohol dependence. Thus, in subjects considered to be in full remission, no symptoms of dependence were present. Consistent with DSM-IV, subjects with partial remission had one or two

symptoms of dependence and/or one or more symptoms of DSM-IV alcohol abuse (American Psychiatric Association, 1994; p.180). When tremors were required in the baseline interview, they were also required at follow-up.

Bivariate between-group statistical comparisons were made with the chi-square test except when the expected cell size fell below five, in which case Fisher's exact test was used. Adjusted odds ratios (OR) and associated 95% confidence interval (CI) were derived from linear logistic regression models of the risk for 1-year chronicity of DSM-IV alcohol dependence. The odds ratios were adjusted for age, gender, race and marital status. Except where indicated, odds ratios shown were derived from models with adequate to excellent goodness of fit, as indicated by Hosmer and Lemeshow goodness of fit tests that yielded p values greater than .05.

Results

Of the 130 subjects meeting full criteria for DSM-IV alcohol dependence in this sample, 96.1% reported the DSM-IV physiological specifier (tolerance, withdrawal or both); only five subjects did not. Of those with the specifier, 64.8% had either a full or partial remission at the follow-up interview, while only 20% (one out of the five) without the specifier had full or partial remission (Table 1). There was no significant difference between subjects with and without this specifier in their probability of remission from DSM-IV alcohol dependence by the follow-up interview. In this sample, 68.5% reported tolerance as part of their current DSM-IV alcohol dependence, 72.3% reported alcohol withdrawal as defined in DSM-IV, and 44.6% reported both tolerance and withdrawal. Of those reporting tolerance, 64.0% had either a full or partial remission from DSM-IV alcohol dependence by the follow-up interview, compared to 61.0% of those without tolerance, not a significant difference. Of those reporting withdrawal as defined in DSM-IV, 57.4% had a full or partial remission, compared to 77.8% of those without withdrawal. This difference was statistically significant (p = .03). Requiring both withdrawal and tolerance also produced a significant difference in outcome. Of the subjects with both, 51.7% had full or partial remission, compared to 72.2% who did not have both, a statistically significant difference (p = .016).

TABLE 1. One-year follow-up status of subjects with DSM-IV alcohol dependence at baseline (N= 130[a]), by aspects of the DSM-IV alcohol physiological specifier

Comparison	% remitted at follow-up[b]	p
Physiological specifier		
Yes (125)	64.8	NS
No (5)	20.0	
Tolerance		
Yes (89)	64.0	NS
No (41)	61.0	
Withdrawal		
Yes (94)	57.4	.03
No (36)	77.8	
Both tolerance and withdrawal		
Yes (58)	51.7	.016
No (72)	72.2	
All subjects who had withdrawal: tremors		
With tremors (18)	33.3	.02
Without tremors (76)	63.2	
All *untreated* subjects who had withdrawal: tremors		
With tremors (16)	37.5	.046
Without tremors (68)	64.7	

[a]N size varies for some comparisons, depending on subgroups of interest in the comparison.
[b]Full or partial remission.

When a requirement for tremors was added to the definition of withdrawal, the sample size was reduced to 113; therefore, adding the tremors requirement decreased the number of subjects meeting criteria by about 13%. This occurred because a number of the 130 subjects had received a current diagnosis of DSM-IV alcohol dependence based on the withdrawal criterion and only two other criteria. When the tremors requirement was added, some of these subjects were no longer rated as having withdrawal; this reduced the number of criteria they met to only two, below the threshold for the DSM-IV diagnosis of dependence.

Of the 113 subjects, 54.0% were rated as having withdrawal including the tremors requirement. Among subjects with withdrawal including tremors at baseline, 49.2% of the

TABLE 2. Risk (odds ratios) of 1 -year chronicity of subjects with DSM-IV alcohol dependence at baseline (total N = 130[a]), by aspects of the DSM-IV alcohol physiological specifier: Logistic regression models[b]

	Risk for 1-year chronicity Odds ratios (95% confidence intervals)				
	Physiological specifier	Tolerance	Withdrawal	Both tolerance and withdrawal	All subjects who had withdrawal: tremors
Tremors is not required	0.15(0.02-1.53)	0.96 (0.44-2.11)	2.61(1.05-6.54)	2.52(1.19-5.33)	3.11(1.02-9.42)
Tremors is required	0.51 (0.10-2.58)	0.67(0.27-1.64)	4.48(1.81-11.13)	3.68(1.57-8.61)	2.27 (0.68-7.57)

[a]N size varies for some comparisons, depending on subgroups of interest in the comparison.
[b]Controlled for gender, age, race and marital status.

TABLE 3. One-year follow-up status of untreated subjects with DSM-IV alcohol dependence at baseline (total $N = 118^a$), by aspects of the DSM-IV alcohol physiological specifier: Logistic regression models[b]

	Risk for 1-year chronicity, subjects not in treatment Odds ratios (95% confidence intervals)				
	Physiological specifier	Tolerance	Withdrawal	Both tolerance and withdrawal	All subjects who had withdrawal: tremors
Tremors is not required	0.17(0.02-1.87)	0.91(0.39-2.11)	2.90(1.07-7.81)	2.48(1.12-5.51)	2.71(0.85-8.66)
Tremors is required	0.79(0.12-5.06)	0.61 (0.23-1.61)	5.98(2.11-16.96)	3.88(1.52-9.93)	1.86(0.51-6.80)

[a] *N* size varies for some comparisons, depending on subgroups of interest in the comparison.
[b] Controlled for gender, age, race and marital status.

subjects with withdrawal had full or partial remission, compared to 78.9% of those without withdrawal at baseline defined in this manner ($p = .001$).

Table 2 shows the results of the multivariate predictions of outcome, with and without the requirement of tremors in withdrawal. As shown in Table 2, neither the physiological specifier (tolerance *or* withdrawal) nor tolerance alone significantly predicted 1 -year chronicity of DSM-IV alcohol dependence. However, adjusting for age, gender, race and marital status, withdrawal was a significant predictor (adjusted odds ratio[AOR] = 2.61). As shown in Table 2, both the magnitude and significance of the association were strengthened considerably when tremors were required, even though the sample size was reduced (AOR = 4.48). A variable in which both elements of the physiological specifier were required was a significant predictor of outcome, but was weaker than withdrawal because of the inclusion of tolerance, which had no relation to outcome. While the models for the physiological specifier (tolerance *or* withdrawal) and for the requirement of both tolerance and withdrawal did not adequately fit the data according to the Hoshmer and Lemeshow tests, the remaining models in the table did have an adequate fit to the data.

Considering only the subjects with DSM-IV alcohol dependence at baseline who also had withdrawal produced similar results. Of the alcohol dependent subjects with current withdrawal at baseline, 18 had tremors while 76 did not. Among the subjects with tremors, only 33.3% were in a full or partial remission by the follow-up interview, compared to 63.2% of the subjects whose withdrawal was not accompanied by tremors. This difference was statistically significant ($X^2 = 5.30$, 1 df, $p = .02$). The adjusted odds ratio for risk of 1-year chronicity was 3.43 (95% CI: 1.16 - 10.15). Thus, even with the reduced sample size, the effect size was similar and significant.

At times, investigators wish to know the nature of results from the study when all subjects who have had treatment in the relevant time frame are removed from the sample. Accordingly, we re-did the analysis on the effect of tremors after removing the 12 subjects who had withdrawal and who had had treatment in the 12 months prior to the baseline interview. The results proved to be quite similar when the subjects who had had treatment were removed from the sample.

Of those with physiological specifier, 66.7% had either a full or partial remission at the follow-up interview, while only 25% (one out of four) without the specifier had full or partial remission. There was no significant difference between subjects with and without this specifier in their probability of full or partial remission from DSM-IV alcohol dependence by the follow-up interview. Of those reporting tolerance, 66.2% had either a full or partial remission from DSM-IV alcohol dependence by the follow-up interview, compared to 63.2% of those without tolerance, not a significant difference. Of those reporting withdrawal as defined in DSM-IV, 59.5% had a full or partial remission, compared to 79.4% of those without withdrawal. This difference was statistically significant ($p = .04$). Requiring both withdrawal and tolerance also produced a significant difference in outcome. Of the subjects with both, 54.0% had full or partial remission, compared to 73.5% who did not have both, a statistically significant different ($p = .003$).

When a requirement for tremors was added to the definition of withdrawal, the sample size was reduced to 101. Among subjects with withdrawal including tremors at baseline, 50.0% of the subjects with withdrawal had full or partial remission, compared to 81.6% of those without withdrawal at baseline defined in this manner (p = .001).

Table 3 shows the results of the multivariate predictions of outcome when subjects who had treatment were removed from the sample. As shown in Table 3, neither the physiological specifier (tolerance or withdrawal) nor tolerance alone significantly predicted 1-year chronicity of DSM-IV alcohol dependence that was current at baseline. However adjusting for age, gender, race and marital status, withdrawal was a significant predictor. Consistent with Table 2, both the magnitude and significance of the association were strengthened considerably when tremors were required, even though the sample size was reduced (AOR = 2.90 when tremors were not required, AOR = 5.98 when tremors were required).

Discussion

In this prospective study, we found no evidence for special importance or prognostic meaning of the physiological specifier of alcohol dependence as defined in DSM-IV. However, DSM-IV alcohol withdrawal did predict chronicity. This was

the case in bivariate analyses as well as multivariate analyses that controlled for demographic characteristics ordinarily associated with longitudinal course of the disorder. When the DSM-III and DSM-III-R requirement for tremors was reintroduced into the definition of withdrawal, withdrawal became a stronger and more efficient predictor of chronicity, showing a significant relationship even though the sample size was reduced.

The present study was conducted with a number of methodological improvements over previous longitudinal research on this issue. We clearly classified subjects for current DSM-IV alcohol dependence at baseline, and therefore did not include subjects without a current diagnosis, who would not be relevant to the research questions. We also measured outcome in terms of the course of the same disorder, DSM-IV alcohol dependence, rather than in terms of related but different conditions. The fact that the present findings emerged even though the sample was relatively small supports the use of such methods in longitudinal research. The fact that the results were consistent with Schuckit et al. (1998) lends further support to the validity of withdrawal, but not tolerance, as a physiological specifier.

Unlike the measure of withdrawal suggested by Langenbucher and colleagues (1997), the AUDADIS measure of withdrawal was quite short, had a simple structure and, yet, was still predictive. The addition of the tremors requirement strengthened the predictive ability of the measure without requiring additional interviewing time. Clearly, replication of the results, either in a new sample or in the present sample after a longer period of follow-up, would increase confidence in the findings. However, the current findings appear to indicate that a longer or more complex measure of withdrawal is not needed unless the information is required for a special purpose rather than assigning diagnoses of alcohol dependence.

We have not been able to find documentation of the basis for changing the definition of withdrawal between DSM-III-R and DSM-IV. Perhaps this change went largely unnoticed because the CIDI, the instrument used to collect the data for the DSM-IV field trials and other clinical nosologic studies cited above (Carroll et al., 1994; Langenbucher et al., 1997) defined alcohol withdrawal without requiring tremors, regardless of whether the criteria set was DSM-III-R or DSM-IV. Thus, when using this instrument, rates of alcohol withdrawal based on DSM-III-R and DSM-IV would not show the type of difference that was apparent in the present study.

Often, when longitudinal and cross-sectional findings on validity disagree, longitudinal findings are given precedence in interpretation because longitudinal course implies prognosis. An example of this occurred in the DSM-IV substance disorder work group, when a severity indicator for dependence based on a count of positive criteria was discarded because cross-sectional studies supported the validity of the severity indicator while longitudinal studies did not. Based on earlier longitudinal studies, such a disagreement appeared to occur in the case of the importance of the physiological specifier and its two components. However, the findings of the present study bring longitudinal and cross-sectional findings into closer agreement, at least on the importance of withdrawal.

If clinical relevance is inferred by poor course, then the requirement of tremors appears to offer a more clinically relevant definition of alcohol withdrawal than a definition without such a requirement. However, further work on this issue is needed, in both general population and clinical samples.

This study provided information only on the relationship of the physiological specifier to the diagnosis of alcohol dependence. The results are not necessarily applicable to other substances that have different withdrawal syndromes (or possibly no physiological withdrawal at all). Longitudinal research on subjects who are clearly diagnosed with specific DSM-IV drug disorders at baseline and then followed to determine the course of the specific drug disorders would provide the relevant information. Arriving at an adequate definition of a physiological specifier that applies equally well to all substances may not prove possible, but this should not reduce the importance of identifying a potentially valid physiological specifier for a particular substance. The present study does suggest that changes in components of withdrawal should be considered with care, and backed up with empirical evidence wherever possible.

Some investigators may find the lack of stability in the diagnosis of DSM-IV alcohol dependence surprising, based on the assumption that alcohol dependence is usually a chronic condition. From the standpoint of a clinician working in a treatment setting where chronic cases are the rule rather than the exception, this would be an expected reaction. However, as was described several years ago (Cohen and Cohen, 1984), relying entirely on treated samples for a picture of natural history may be misleading, since such samples may be biased by many factors. We conducted this study in a community sample for exactly these reasons.

Along the same lines, some investigators may find the high proportion of alcohol dependent subjects who reported withdrawal surprising. However, recall that all these subjects reported at least two other dependence symptoms, and their ethanol consumption levels were quite high, on average (Hasin and Liu, in preparation). A great deal of psychopathology in the general population goes untreated, as has been demonstrated repeatedly in epidemiologic surveys. This evidently applies to specific symptoms of alcohol dependence as well as to the diagnosis itself.

We did not obtain a significant difference in follow-up status between those who had the physiological specifier as defined in DSM-IV and those who did not when tremors was not required as part of the withdrawal criteria. The Fisher's exact test was at the level sometimes considered to be of

borderline significance for the opposite result (e.g., a beneficial effect of the physiological specifier). However, the number of subjects without the physiological specifier was so small that we do not feel that anything should be made of this nonsignificant result. We could speculate about various explanations, but feel that such speculation should await replication by other investigators.

A larger proportion of the subjects with DSM-IV alcohol dependence reported withdrawal than tolerance. The biological mechanisms underlying withdrawal and tolerance and their relationships are complex and not yet completely understood. Therefore, the implications of this difference in proportions is unclear. The degree to which this generalizes to other samples, or to other drugs, deserves future research attention.

Clinicians may be concerned that re-introducing restrictions into a diagnostic category would deprive patients of needed care. According to this concern, a more restricted definition of a given disorder would result in fewer diagnoses being made, thus potentially limiting the clinical attention given to patients or the insurance reimbursement they are entitled to receive. Of course, invalid restrictions would produce exactly this unfortunate result. At the same time, a diagnosis that is overly inclusive may result in a general failure to take the disorder seriously in clinical settings, and may also result in a dilution of research findings. Concerning the importance of tremors as a requirement in alcohol withdrawal, we do not feel that the present study settles the issue. However, perhaps it will stimulate further work. An accumulation of findings from different studies with adequate designs would provide a sounder basis for decision-making.

Some limitations of the study include the fact that the sample was small and the length of follow-up was only about 1 year. A longer period of follow-up would provide valuable additional information about the stability of the results. However, advantages of the study include the clear indication of current diagnostic status at baseline, the unbiased nature of the sample, and the direct relevance of the outcome measure, which was the disorder in question. We hope that these results are heuristic for future studies of the physiologic specifier of substance dependence.

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