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RESEARCH REPORT

The histories of withdrawal convulsions and delirium tremens in 1648 alcohol dependent subjects

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Abstract

A small proportion of alcohol-dependent men and women experience delirium tremens (DTs) and/or convulsions during alcohol withdrawal. While some characteristics of individuals most likely to show these severe sequelae of the abstinence syndrome have been described, it is not clear whether these risk factors operate independently in their association with severe withdrawal. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview was used to evaluate 1648 alcohol dependent men and women (including 540 women). The background characteristics and drinking histories of the 160 men and 51 women (12.8% of the subjects) who reported ever having had at least one episode of DTs and/or convulsions during withdrawal were compared with the characteristics of the remaining alcohol dependent individuals. Compared to other alcohol-dependent subjects, those with histories of severe withdrawal reported a greater maximum number of drinks in any 24-hour period (40.9 ± 25.71 versus 24.9 ± 17.72), more withdrawal episodes (28.2 ± 33.74 versus 15.9 ± 26.84), more non-medicinal use of sedative–hypnotics (56.4% versus 32.9%) and a greater number of medical problems. Hierarchical logistic regression analysis revealed that the most powerful differences between those with histories of more and less severe withdrawals related to the maximum number of drinks per day and the total number of withdrawal episodes. The remaining variables still added significantly to the relationship to more severe withdrawal. The etiology of DTs and convulsions is complex and involves the interaction of diverse characteristics representing relatively unique domains. It is hoped that these data will help clinicians identify individuals most likely to have experienced severe withdrawal syndromes and will aid researchers attempting to understand more about the etiology of these problems.

Introduction

Our understanding of the diagnostic criteria and appropriate treatments of alcohol withdrawal has increased in recent years (Sellers & Kalant, 1976; Sellers *et al.*, 1991). This syndrome consists of signs of autonomic nervous system hyperactivity, anxiety, insomnia and other symptoms that are the opposite of the acute effects of brain depressant administration (American Psychiatric Association, 1994; Schuckit, 1995). Despite

The Collaborative Study on the Genetics of Alcoholism (COGA) (H. Begleiter, SUNY HSCB Principal Investigator, T. Reich, Washington University, Co-Principal Investigator) includes six different centers where data collection takes place. The six sites and Principal Investigator and Co-Investigators are: Indiana University (J. Nurnberger Jr, P. M. Conneally); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego and Scripps Institute (M. Schuckit, F. Bloom); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (H. Begleiter, B. Porjesz); Washington University in St Louis (T. Reich, C. R. Cloninger). This national collaborative study is supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) by USPHS grants NIAAA U10AA08401, U10AA08402, U10AA08403.

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earlier hypotheses to the contrary, the withdrawal phenomena appear to relate primarily to a history of repeated heavy exposure to alcohol followed by relative or absolute abstinence, and are not just the ramifications of poor nutrition or organ damage (Isbell *et al.*, 1955; Salum, 1972; Sellers *et al.*, 1991).

Recent studies have demonstrated that the usual alcohol withdrawal or abstinence syndrome is relatively mild. Thus, in an evaluation of 487 hospitalized alcohol-dependent individuals, only 10.6% demonstrated withdrawal syndromes judged to be severe enough to require medications (Benzer, 1990). Also, several investigations have indicated that the alcohol withdrawal syndrome is usually mild enough to be treated on an outpatient basis (Feldman, Pattison & Subell, 1975; Hayashida *et al.*, 1989; Schuckit, 1995). One study of 1024 patients undergoing evaluation for outpatient detoxification identified only 90 (8%) who were felt to demonstrate severe enough syndromes to require hospitalization (Whitfield, Thompson & Lamba, 1978).

The corollary of these findings, however, is that 10% or so of alcohol-dependent individuals are likely to develop more severe withdrawal syndromes at some time in their lives. These potentially dangerous conditions include a combination of marked autonomic nervous system overactivity such as large increases in blood pressure, pulse, respiratory and heart rates, along with an elevated body temperature, sweating and a severe tremor. Among the more intense withdrawal conditions that can be seen in conjunction with autonomic hyperactivity, the most dramatic is delirium tremens (DTs) (Nordstrom & Berglund, 1986). While there is some disagreement about the optimal definition of this condition (which is cited in DSM-IV as Alcohol Withdrawal Delirium (American Psychiatric Association, 1994)), most studies agree that in addition to evidence of severe autonomic dysfunction patients must show some level of confusion or disorientation, often accompanied by illusions, hallucinations and agitation (Hemmingsen, Kramp & Rafaelsen, 1979; Kramp, Ronsted & Hansen, 1979; Tonnesen, 1982; Pycha *et al.*, 1993). This type of severe withdrawal syndrome begins within the first several days of withdrawal, peaks in intensity between days three and four, and is likely to markedly improve over a 72-hour period (Isbell *et al.*, 1955; Salum, 1975; Hemmingsen *et al.*, 1979; Kramp *et al.*, 1979; Pycha *et al.*, 1993). Past studies of severe DTs indicated a mortality rate of 15–25%, but more modern clinical experience indicates that the death rate associated with DTs is relatively low, perhaps 1% or less (Victor, 1966; Thompson, Johnson & Maddrey, 1975; Pycha *et al.*, 1993; Schuckit, 1995)).

Most authors agree that DTs are relatively rare, with the prevalence varying with the definition used. For example, when less restrictive criteria are invoked that do not require high levels of clinical impairment or when only patients with very severe and long-lasting intoxications are considered, as many as 20–40% of alcoholics can show some symptoms of this condition (Isbell, 1955; Salum, 1972). However, most clinical reviews indicate that the lifetime risk that an alcohol-dependent individual will ever have a full-blown DT condition is between 5% and 10% (Hemmingsen *et al.*, 1979; O'Connor *et al.*, 1993; Schuckit *et al.*, 1993; Tsuang *et al.*, 1994).

The second type of severe alcohol withdrawal state involves one or more *grand mal* convulsions, a complication that can be observed during withdrawal from any brain depressant (Pieninkeroinen, Telakivi & Hillbom, 1992; Schuckit, 1995). Most studies indicate that convulsions are only reported in the lifetime histories of between 5% and 10% of alcohol-dependent individuals (Brown *et al.*, 1988; O'Connor *et al.*, 1991, 1993; Schuckit *et al.*, 1993). Slightly higher rates might be observed among alcohol-dependent men and women with excessively high levels of alcohol intake over relatively longer periods of time (Isbell *et al.*, 1955; Victor & Adams, 1953). When convulsions occur as part of withdrawal, they are likely to be seen after many years of heavy drinking (Schuckit *et al.*, 1993, 1995).

Most reviews agree that the likelihood of DTs and/or convulsions during withdrawal from alcohol increases with higher levels of alcohol intake over longer periods of time (Isbell *et al.*, 1955; Goldstein, 1972; Pristach, Smith & Whitney, 1983; Vinson & Menezes, 1991; Becker & Hale, 1993). However, there is less consensus about other factors that correlate with, or perhaps contribute to, these severe withdrawal phenomena. One set of theories especially relevant to convulsions involves kindling. As defined by Goddard, McIntyre & Leech (1969), kindling is

a condition where the brain is likely to demonstrate progressively more severe motor overactivity following repeated less intense (subthreshold) electrical stimulations in the past. This is relevant to alcohol because withdrawal states are associated with evidence of higher levels of brain activity as measured by brain wave patterns, glucose utilization and, for at least one study, by evidence of increased cerebral blood flow—although not all authors agree (Begleiter, Gross & Porjesz, 1973; Brown *et al.*, 1988; Hemmingsen *et al.*, 1988; Caspari *et al.*, 1993). Both animal and human studies indicate a greater likelihood of severe withdrawal symptoms in individuals who have had a greater number of withdrawal episodes in the past (Ballenger & Post, 1978; Baker & Cannon, 1979; Clemmesen & Hemmingsen, 1984; Ulrichsen, Clemmensen & Hemmingsen, 1992, Becker & Hale, 1993). The specific neurochemical mechanisms for the central nervous system (CNS) hyperactivity are not well understood, but at least one author feels these changes might relate to supersensitivity or upregulation of the N-methyl-D-aspartate (NMDA) receptors as a consequence of prior inhibition of this receptor complex by alcohol (Morrisett *et al.*, 1990).

In addition to higher quantities of alcohol and kindling, a third domain of potential predictors and correlates of more severe withdrawal involves evidence of additional medical conditions and associated physiological problems. One theory relates to the relatively consistent finding that more intense withdrawal symptoms are associated with high levels of body water and possible brain edema (Trabert *et al.*, 1992). Other physiologically related hypotheses of severe alcohol withdrawal states involve changes in electrolytes, especially potassium or magnesium, the possibility that any severe medical condition can markedly increase the intensity of the withdrawal symptoms (Tonnensen, 1982; Pycha *et al.*, 1993) and that vitamin deficiencies might play a role (Nordentoft *et al.*, 1993). However, at least one clinical study demonstrated convulsions and DTs in healthy well-nourished individuals who developed their severe alcohol dependence as part of a scientific experiment (Isbell *et al.*, 1955).

Finally regarding risk factors, several investigations indicate a greater likelihood of severe withdrawal among alcohol-dependent individuals who have had exposure to other drugs of abuse (Schuckit, 1993). There is also some evidence that the more severe signs of withdrawal, including DTs and convulsions, are most likely to be observed among individuals who receive inadequate pharmacological treatment for their alcohol withdrawal (Kaim, 1971; Pycha *et al.*, 1993).

In summary, the alcohol withdrawal syndrome is usually relatively mild. A number of factors have been hypothesized to be associated with more severe problems in withdrawal, including a higher quantity of alcohol intake, a greater number of prior withdrawal episodes, medical problems and exposure to additional drugs. The relative rarity of these severe withdrawal syndromes and the associated need for large clinical samples makes it difficult to determine which, if any, of these factors are most relevant to DTs and convulsions. Further clouding the issue is the possibility that some factors such as higher levels of medical impairment might only be correlates or consequences of the heavy alcohol and drug use and not contribute directly to the DTs or convulsions themselves. This study evaluates the histories of DTs and convulsions in a large sample of carefully studied alcohol-dependent individuals. The goal is to establish the prevalence, clinical correlates and possible physiological contributors to the syndrome while controlling for the potential impact of the level of alcohol intake.

Methods

The data were gathered as part of the ongoing Collaborative Study on the Genetics of Alcoholism (COGA) study. As described elsewhere, six research centers in different parts of the United States have standardized their procedures to identify alcohol dependent probands using DSM-III-R and other diagnostic criteria as part of a pedigree study (Bucholz *et al.*, 1994; Schuckit *et al.*, 1994). The investigation uses the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a reliable standardized instrument that gathers information on demography, alcohol and drug use patterns, and major psychiatric disorders (Bucholz *et al.*, 1994), to evaluate all available appropriate alcohol-dependent (alcoholic) probands and their first- and second-degree relatives. In addition control subjects, chosen through a variety of mechanisms in

different sites including random mailings, driving records, random telephone calls and individuals presenting to medical and dental clinics (Schuckit *et al.*, 1995).

The SSAGA uses questions originally derived from the Diagnostic Interview Schedule (DIS), the Composite International Diagnostic Instrument–Substance Abuse Module (CIDI–SAM) and the Structured Clinical Interview for DSM-III-R (SCID) and other instruments to establish DSM-III-R dependence on alcohol and other drugs as well as major psychiatric disorders (Bucholz *et al.*, 1994). The alcohol use section of the interview also queries individuals about their lifetime history of periods of withdrawal syndromes. A specific question regarding withdrawal convulsions is asked as: "When you stopped, cut-down, or went without drinking, did you have fits, seizures, or convulsions where you lost consciousness, fell to the floor, and had difficulty remembering what happened?" A history of delirium tremens at any time in the past is established by asking: "Did you have the DTs; that is a condition where you were very confused, extremely shaky, felt very frightened or nervous, or saw things that weren't really there when you stopped, cut-down, or went without drinking?" For the purposes of the evaluations reported here, alcohol-dependent subjects were divided into those who demonstrated evidence of DTs and/or convulsions during any withdrawal episode versus those who did not.

Statistical analyses were carried out by comparing DSM-III-R alcohol-dependent individuals with and without evidence of DTs and/or convulsions using Student's *t*-test for continuous variables and chi-square for categorical data. Regression analyses were carried out to test the contribution of variables of interest while controlling for important covariates. Because the dependent variable is dichotomous, PROC LOGISTIC (SAS) was used to analyse multivariate relationships. For these analyses, in an effort to test a specific model suggested from the review of the literature, three items were extracted first and then the potential importance of several additional factors were tested. The three initial variables included the maximum drinks in 24 hours, the total number of withdrawal episodes and a measure of five medical symptoms related to alcohol including liver disease, gastritis, pancreatitis, cardiomyopathy and peripheral neuropathy.

Results

From February 1991 to March 1994, 3395 alcoholics, controls and relatives were evaluated with the SSAGA across the six centers. From this group, the 1648 interviewed alcohol-dependent individuals were queried regarding their alcohol withdrawal histories. This sample consists of 548 alcoholic probands (33.2%) recruited from alcohol treatment facilities, 992 relatives of probands (60.2%), as well as 108 controls who were discovered to be alcohol dependent and similarly diagnosed relatives of controls (6.6%). The 1648 interviewed alcohol-dependent men and women had a mean age of 37.9 ± 12.54 (mean $\pm$ SD) years, 540 were female (32.8%), and the mean educational level was 12.6 ± 2.34 years. The majority (76.8%) were Caucasian, 14.8% black and 5.8% Hispanic with 2.7% Asian or other. With respect to marital status, at interview 30.9% were single, 43.9% married and the remainder divorced (16.4%), separated (7.2%) or widowed (1.6%). These men and women had an onset of clustering of alcohol problems (i.e. the age they first met DSM-III-R criteria for alcohol dependence) at an average age of 24.4 ± 8.73 years.

By self-report, 188 of these individuals (11.4%) ever experienced DTs, including 31 subjects (1.9% of the total sample and 16.5% of those with DTs) who ever had a *grand mal* convulsion during withdrawal. Another 23 subjects (1.4% of the total) had histories of convulsions, but no episodes of DTs. Thus, a total of 211 individuals (12.8%) reported DTs and/or convulsions. The relatively low number of individuals reporting convulsions in the absence of DTs contributed to the decision to combine all 211 subjects into one group who had demonstrated a severe withdrawal syndrome (DTs and/or convulsions). The small proportion of alcohol-dependent subjects with severe withdrawal also argued for combining data for the 160 men and 51 women in the severe withdrawal group. The major analyses reported in Tables 5 and 6 did not differ significantly across the two sexes.

The 211 individuals with histories of severe withdrawal had an average of 5.8 ± 7.01 episodes of DTs or convulsions in the past, with a range from 1 (for 29.4% of the 211) to 45. Most (60.7%) subjects in the group had five or fewer episodes of convulsions or DTs, and 85.3% had 10 or fewer. For those with convulsions only,

Table 1. *Demographic and diagnostic characteristics for 1648 alcohol-dependent individuals with and without a history of severe withdrawal*

	History of DTs and/or convulsions	
Demographic and diagnostic characteristics	Yes	No
Number of subjects	211	1437
Age at interview (years)	40.2 ± 12.23	37.5 ± 12.56†
Education (years)	12.0 ± 2.15	12.7 ± 2.35‡
Gender (% male)	75.8	65.9†
Race (%)		
Caucasian	73.5	77.3
Black	18.9	14.1
Hispanic	5.7	5.8
Asian/other	1.9	2.8
Marital status (%)		
Single	29.4	31.1
Married	32.2	45.7‡
Separated	11.4	6.5*
Divorced	25.6	15.1‡
Widowed	1.4	1.6
Psychiatric Diagnoses (DSM-III-R) (%✓)		
Alcohol dependence	54	64.0†
Antisocial personality disorder	25.6	14.7‡
Any substance dependence (other than alcohol)	48.8	31.5‡
Major depressive disorder	9.9	12.3

* Test statistic for comparison is significant at $p < 0.05$.
† Test statistic for comparison is significant at $p < 0.01$.
‡ Test statistic for comparison is significant at $p < 0.001$.
✓ These diagnoses are given to indicate the primary or chronologically first appearing psychiatric disorder.

there was an average of 3.6 ± 4.19 periods of convulsions in the past, with a range of 1–20. Those with DTs reported an average of 5.2 ± 6.06 episodes in the past, with a range of 1–25. The subjects with histories of severe withdrawal had their first episode of any type of withdrawal at age 28.8 ± 9.64 years, while the 36.3% of the 1437 remaining subjects who had experienced some type of withdrawal episodes had their first withdrawal at age 29.3 ± 10.04 years ($t = 0.66$, 380 df, $p = 0.5$).

The tables display the clinical and demographic correlates of the 211 individuals with more severe withdrawal (i.e. a history of convulsions and/or DTs) compared to those without such histories. Table 1 reveals several significant differences between the two groups on demographic characteristics. Those with more severe withdrawal were more likely to be male, were significantly older, somewhat less educated, and more likely to be separated or divorced. A higher percentage of the DT and/or convulsion group met criteria for the antisocial personality disorder or had a history of dependence on drugs other than alcohol, a finding which is amplified upon in Table 2. These data also reflect the lower proportion of primary alcoholics in the more severe withdrawal group.

Table 3, comparing the two groups on their alcohol use and problem histories, reveals that those with DTs and/or convulsions in the past reported a greater number of years of heavy drinking (i.e. the time since the onset of alcohol dependence but exclusive of abstinence periods), higher patterns of alcohol intake in both recent months and before, a greater number of alcohol-related lifetime problems taken from the SSAGA list of 52 items and from the nine items for dependence in DSM-III-R, and a higher lifetime number of prior withdrawal episodes. The DT/convulsion group also had a longer-lasting and more intense prior withdrawal episodes.

As shown in Table 2, another characteristic of those with histories of severe withdrawal was a self-report of higher levels of involvement with substances other than alcohol. This included a greater likelihood of ever having used a drug IV and a larger number of types of substances used,

Table 2. *Substance use and diagnostic histories for 1648 alcohol—dependent individuals with and without a history of severe withdrawal*

	History of DTs and/or convulsions	
Substance use and diagnoses	Yes	No
Number of subjects	211	1437
Number of different substances used	2.2 ± 1.89	1.5 ± 1.52‡
Substances used more than 10 times (% lifetime)		
Amphetamines	49.8	39.1†
Cannabionls	79.2	78.2
Cocaine	59.7	51.7
Opiates	47.4	26.2‡
Sedative–hypnotics§	56.4	32.9‡
Intravenous use of any drug	18.0	7.9‡
DSM-III-R substance dependence (% lifetime)		
Amphetamines	21.3	10.9‡
Cannabinols	42.7	28.3‡
Cocaine	38.9	23.6‡
Opiates	16.6	6.3‡
Sedative–hypnotics	19.4	6.9‡

* Test statistic for comparison is significant at $p < 0.05$.
† Test statistic for comparison is significant at $p < 0.01$
‡ Test statistic for comparison is significant at $p < 0.001$
§ included in hierarchical logistic regression analysis (Table 5).

especially amphetamines, opiates and sedative–hypnotics. Those subjects reporting severe withdrawal from alcohol more often met DSM-III-R criteria for dependence on amphetamines, cannabinols, cocaine, opiates and sedatives. While not shown in the tables, subjects were also asked to estimate the number of times in the past they had taken each of the types of drugs of abuse. In general, the two groups of subjects were similar on the number of times they reported having used amphetamines, cocaine, opiates and sedative–hypnotics, but reported significantly different levels of intake for cannabinols (488.0 ± 459.4 times versus 369.2 ± 432.1 times for the more severe and less severe withdrawal groups; $t = -3.13$, $p < 0.01$).

Table 4 compares the two groups on medical and psychiatric histories. Those with more severe withdrawal were more likely to report overall poor health, evidence of a variety of physical disorders, most of which resulted from alcohol use, and exhibited symptoms of psychiatric problems related to alcohol use. In Table 4, the psychiatric symptoms are placed in quotation marks because they deal with symptoms felt by the subject to have caused concern, but not necessarily DSM-III-R diagnosable syndromes. These questions were assessed as a part of the overall evaluation of alcohol dependence and related experiences.

Table 5 explores the relationship among those variables from the previous tables that distinguish between more and less severe withdrawal groups. Based on the review of the literature, it was hypothesized that three characteristics were likely to explain most of the differences between the two groups, with the remaining findings possibly reflecting consequences of those three. Table 5 presents the results of a hierarchical regression analysis where the lifetime maximum number of drinks in 24 hours, the total number of episodes of withdrawal and a count of the medical conditions from Table 4 were evaluated, in that order, as they impacted on the ability to distinguish between more and less severe withdrawal groups. Each of these three phenomena contributed significantly and independently to the presence of severe withdrawal, with the three resulting in a significant model (likelihood ratio $\chi^2 = 325.62$, 3 df, $p < 0.0001$), from which an estimate of the variance explained ($R^2 = 0.025$) was calculated (Maddala, 1983). The three initial items in Table 5 were also examined in light of the differences in demographic background described in Table 1. Thus, gender, age and years of drinking

Table 3. *Alcohol use and problem histories for 1648 alcohol-dependent individuals with and without a history of severe withdrawal*

	History of DTs and/or convulsions	
Alcohol use and problems	Yes	No
Number of subjects	211	1437
Age of onset of alcohol dependence	24.2 ± 8.85	24.4 ± 8.72
Years of heavy drinking (excl. abstinence periods)	13.4 ± 9.76	9.9 ± 9.38‡
Days of drinking per week (drinkers, last 6 months)	5.9 ± 1.86	4.1 ± 2.21‡
Maximum drinks in 24 hours (lifetime)§✓	40.9 ± 25.71	24.9 ± 17.72‡
Total alcohol use problems reported (of 52)	33.1 ± 6.21	19.1 ± 9.15‡
Total DSM-III-R alcohol dependence criteria (of 9)	8.5 ± 0.89	5.5 ± 1.99‡
Total withdrawal episodes§	28.2 ± 33.74	15.9 ± 26.84‡
Number of withdrawal symptoms (worst episode)	5.9 ± 2.29	4.1 ± 2.02‡
Length of longest withdrawal (days)	5.4 ± 4.65	4.4 ± 4.6†

* Test statistic for comparison is significant at $p < 0.05$.
† Test statistic for comparison is significant at $p < 0.01$.
‡ Test statistic for comparison is significant at $p < 0.001$
§ Included in hierarchical logistic regression analysis (Table 5).
✓ A drink is approximately 10 g of absolute ethanol, or the rough equivalent of 12 oz. beer, 4 oz. glass of non-fortified wine or 1 oz. of 80% proof beverage.

were first entered in a three-variable explanatory model, after which the three correlates from Table 5 were entered. Any contribution of these demographic measures to the presence of severe withdrawal in the sample disappeared after the successive entry of maximum alcohol consumption, number of withdrawal episodes reported and number of medical conditions associated with prolonged alcohol use.

After determining the relationship among these three measures and more severe withdrawal, several additional variables which differentiated between the groups in Tables 2–4 were added to the logistic regression in a similar hierarchical fashion. As is shown in Table 5, two additional measures contributed independently to a history of severe withdrawal. The full five-variable model also manifested a significant relationship to the history of severe withdrawal as gauged by an overall likelihood ratio test ($\chi^2 = 443.31$, 5 df, $p < 0.0001$). Compared to the three-variable model in Table 5, the five-variable approach demonstrated a significant increase in both the likelihood ratio test ($\chi^2 = 117.69$, 2 df, $p < 0.0001$) and in the estimate of variance explained ($R^2 = 0.33$, $\Delta\ R^2 = 0.08$, $p < 0.0001$). Thus, although the history of the maximum alcohol consumption, number of withdrawal episodes and medical conditions account for the majority of the influence of this model, the additional measures presented in Table 5 contribute in a statistically meaningful way to explaining the presence of severe withdrawal among subjects in the sample. Potential interactions between the five items were evaluated, but no statistically significant interactions were found.

Additional variables were tested but not included in the final model because they did not contribute significantly. These items included the presence of a DSM-III-R diagnosis of antisocial personality disorder, dependence on any substance other than alcohol, the number of different illicit substances (other than alcohol) used and the use of any drug intravenously. They had originally been selected for evaluation either because their relevance was suggested by the literature, or as a result of the data reported in the earlier tables. Another variable, the global self-rating of the overall health status, did add a small, but significant increase in the beta weight, but was not used in the model because it conceptually directly overlapped with the number of medical problems.

The data offered in Tables 2–5 can be viewed from the perspective of the clinical relevance of each item for identifying patients most likely to have had severe withdrawal. One approach to this goal is demonstrated in Table 6. Here, each item listed in Table 5 is considered in light of the odds ratio (i.e. the differential risk associated with each unit increase in the relevant measure) multiplied by the average difference for that

Table 4. *Medical and psychiatric symptom histories for 1648 alcohol-dependent individuals with and without a history of severe withdrawal*

Medical and psychiatric symptoms	History of DTs and/or convulsions: Yes	History of DTs and/or convulsions: No
Number of subjects	211	1437
Medical symptoms (%)		
Fair or poor general health	32.7	13.6‡
Head injury	44.6	31.6‡
Liver disease§	27.5	4.5‡
Gastritis§	23.2	5.9‡
Pancreatitis§	9.0	1.0‡
Cardiomyopathy§	4.3	1.0‡
Peripheral neuropathy§	26.1	4.7‡
Psychiatric "symptoms" from alcohol use¶		
Memory problems§	64.9	20.6‡
Feelings of "depression"§	84.4	33.1‡
Feelings of "anxiety"§	74.9	19.6‡
Feelings of "paranoia"§	61.6	16.5‡

* Test statistic for comparison is significant at $p < 0.05$.
† Test statistic for comparison is significant at $p < .01$.
‡ Test statistic for comparison is significant at $p < .001$.
¶ These "symptoms" were felt to be relevant experiences by the respondant, but do not necessarily reflect diagnostically relevant psychiatric syndromes.
§ Included in hierarchical logistic regression analysis (Table 5).

measure between the two groups demonstrated in Tables 2–5. Table 6 reveals that the between-group odds for severe withdrawal is most markedly increased with a larger maximum number of drinks per day and the number of withdrawal syndromes experienced.

Despite the lack of significant gender differences, because the paucity of information on withdrawal phenomena in women, the characteristics by gender are worth a brief review. Comparing the 51 women with histories of severe withdrawal with the 160 men in that category, regarding Table 3 the two groups were not significantly different on age of onset of alcohol dependence (men vs. women of 24.5 ± 8.88 vs. 23.5 ± 8.77 years), years of heavy drinking (excluding abstinence periods) (14.2 ± 10.03 vs. 11.0 ± 8.48), drinking frequency (6.0 ± 1.79 vs. 5.4 ± 2.12 days per week), total number of alcohol problems (33.3 ± 6.23 vs. 32.5 ± 6.18), number of withdrawal symptoms in the worst episode (5.9 ± 2.35 vs. 6.0 ± 2.14) and on the number of days of the longest withdrawal (5.6 ± 4.64 vs. 4.8 ± 4.69). Regarding Table 2, the two sex groups were also similar on the number of different substances used (2.1 ± 1.93 vs. 2.4 ± 1.79), and did not differ on the pattern of exposure to the various drugs listed in Table 2. Men and women with more severe withdrawal were also similar on the medical and psychiatric symptoms on Table 4, but with a trend for women to be more likely to report past symptoms of depression (81% vs. 94%), a difference that is non-significant following Bonferroni corrections.

Discussion

This paper describes a large and demographically heterogeneous sample of alcohol-dependent men and women. Such a large sample is required to generate information on a relatively rare outcome associated with alcohol dependence. The data demonstrate that the lifetime risk of having at least one episode of DTs or convulsions among the 1648 alcohol-dependent individuals was low. Only 3.3% of these men and women had ever experienced a *grand mal* convulsion in the midst of an alcohol withdrawal episode, while 11.4% had a history of DTs during one or more of their withdrawal episodes. A number of these subjects experienced both DTs and convulsions. Thus, even in a sample with an average

Table 5. *Multivariate hierarchical logistic regression analysis of correlates of severe withdrawal in 1648 alcohol-dependent individuals*

Correlate of severe withdrawal	Standardized regression coefficient	χ^2	Odds ratio	95% confidence limits
Maximum drinks in 24 hours (lifetime)	0.2003	20.59‡	1.02	1.01, 1.03
Total withdrawal episodes	0.1187	9.87†	1.01	1.00, 1.02
History of medical conditions (index of 5)	0.3629	68.78‡	1.96	1.67, 2.29
Likelihood ratio $\chi^2 = 325.62$, 3 df, $p < 0.0001$; ~ Model $R^2 = 0.25$				
Ever illicit sedative use (10 + times)	0.1107	5.21*	1.52	1.06, 2.18
Psychiatric symptoms (index of 4)	0.5128	93.56‡	2.27	1.93, 2.69
Likelihood Ratio $\chi^2 = 443.31$, 5 df, $p < 0.0001$; ~ Model $R^2 = 0.33$				
5-Correlate model versus 3-correlate model:				
△ Likelihood ratio $\chi^2 = 117.69$, 2 df, $p < 0.0001$; △ $R^2 = 0.08$, $p < 0.0001$				

* Test statistic is significant at $p < 0.05$.
† Test statistic is significant at $p < 0.01$.
‡ Test statistic is significant at $p < 0.001$.

age of approximately 40 years who had fulfilled the criteria for alcohol dependence for approximately age 16 years, 87% of the subjects had never experienced a severe withdrawal episode.

The literature reveals a relatively short list of characteristics that have been found to correlate positively with a history of severe withdrawal episodes. The present study corroborated the importance of higher levels of drinking, evidence of more severe or pervasive alcohol-related medical problems, and a greater number of withdrawal episodes as important factors associated with more severe withdrawal episodes in the past (Isbell *et al.*, 1955; Becker & Hale, 1993; Caspari *et al.*, 1993; Pycha *et al.*, 1993; Schuckit *et al.*, 1993). However, once these factors are considered, neither demography (including years of alcoholism, gender or educational level) nor a diagnosis of the antisocial personality disorder contributed significantly to the hierarchical logistic regression analyses.

It was not clear from the literature review which, if any, of the major factors associated with a history of more severe withdrawal added independently to the findings. It was possible, for example, that the impact of the total number of withdrawal episodes might disappear after considering the history of the quantity of alcohol intake, or that the importance of drugs other than alcohol might diminish significantly after considering medical symptoms. However, the logistic regression analyses revealed that each of the major factors outlined in Table 5 relates significantly to a history of DTs or convulsions. All factors combined explain one-third of the variance of the ability of the logistic regression to distinguish between those with and those without histories of severe withdrawal episodes.

The present results are consistent with the potential importance of kindling as a mechanism contributing to the higher risk for severe CNS disturbances observed in the context of withdrawal syndromes from alcohol (Ballenger & Post, 1978). As predicted, a history of DTs and/or convulsions was associated with a greater number of withdrawal episodes. The present study is not a perfect test of the phenomenon because data were only collected on the total number of withdrawal episodes, not on the number of withdrawals that preceded the withdrawal seizure. None the less, the data from this large and diverse sample of alcohol-dependent men and women indicate that further work on kindling could be important in enhancing our understanding of severe withdrawal phenomena.

Table 6 indicates that a great deal of the differential between alcohol dependent subjects with and without more severe withdrawal histories can be explained by the intensity of past alcohol intake and the number of withdrawal syndromes experienced. The third major contributor, one that appears to have an important relationship to DTs and/or convulsions even after considering the alcohol intake and the number of episodes of withdrawal, is a measure of medical syndromes. This finding is consistent

Table 6. *Calculated odds of having a history of severe withdrawal among 1648 alcohol-dependent individuals*

Correlate of severe withdrawal Correlate of severe withdrawal	Group score difference	Associated odds ratio	Group odds difference
Maximum drinks in 24 hours (lifetime)	16.00	1.02	16.32
Total withdrawal episodes	12.30	1.01	12.42
Medical symptoms (index of 5)	1.33	1.96	2.61
Ever sedative user (lifetime)	0.24	1.52	0.36
Psychological symptoms (index of 4)	1.52	2.27	3.45
Calculated odds for severe withdrawal based on 5-correlate model			35.16

with the literature and with clinical lore indicating that the more severely medically impaired an individual is, the greater the likelihood that he or she will show signs and symptoms of severe withdrawal conditions. The majority of the items evaluated were likely to have been consequences of repeated high levels of alcohol intake. It is possible that disturbances of potassium or magnesium levels might also have contributed to the seizure risk, but these variables could not be measured in a retrospective study.

The finding in Table 2 that a history of more severe withdrawal episodes was associated with a history of exposure to a wider variety of drugs, especially sedative–hypnotics, was also expected. However, compared to the other variables tested in Tables 5 and 6, only sedative–hypnotic use added significantly to the logistic regression. Perhaps exposure to these drugs altered the CNS sensitivity demonstrated during alcohol withdrawal syndromes. Unfortunately, while the number and ages of inpatient treatment for withdrawal were asked the specific medications used, if any, were not recorded. It is also possible that some of the episodes of withdrawal delirium or convulsions might actually have related to withdrawal states from barbiturates or benzodiazepines which the subject might have erroneously attributed to the alcohol (Garcia-Borreguero *et al.*, 1991; Schuckit, 1995). Finally, the lack of a relationship between severe withdrawal and the use of stimulants such as amphetamines and cocaine might be accurate, but the true test of this question requires prospective studies that incorporate drug toxicology screens.

Individuals with histories of severe withdrawal were significantly more likely to describe symptoms of depression, anxiety, paranoia or severe memory impairment in the past. These were reported by subjects to have related to the alcohol use but could have occurred at other times. This association between an index of psychological symptoms and more severe withdrawal remained robust even after considering the impact of the drinking history, the number of withdrawal episodes, medical conditions, and sedative–hypnotic drug use. There is one other report with a similar finding, at least with regard to anxiety (Johnston *et al.*, 1991). It is possible that a history of psychological problems might indicate individuals whose central nervous system is responding to alcohol withdrawal and intoxication with greater levels of sensitivity overall; or perhaps a kindling-like phenomenon contributes to both an enhanced risk for seizures and longer lasting psychiatric symptoms as part of a more severe protracted withdrawal phase (Roelofs & Dikkenberg, 1987; Satel *et al.*, 1993). While these hypotheses are worth further evaluation, it is also possible that the impact of the psychological symptom might be just another indirect measure of more intense alcohol use or correlates of more severe withdrawal.

In this retrospective study, women were less likely than men to report histories of DTs or convulsions. However, gender did not have any impact on the logistic regression results reported in Tables 5 and 6. The present findings regarding gender corroborate a recent comparison of the two sexes (O'Connor *et al.*, 1993). These two results occurred despite a literature that indicates that alcohol-dependent women might be more likely than their male counterparts to develop alcohol-related brain and liver damage despite fewer years of heavy drinking (Saunders, Davis & Williams, 1981; Mann *et al.*, 1992), although not all studies agree (Ross, 1989). The lack of evidence that women have more severe withdrawal phenomena despite prior work demonstrating a differential risk for medical

problems in men and women underscores the impact of multiple contributors to the withdrawal picture. Thus, it is the combination of five items, not just one variable, that best describes the data in Tables 5 and 6.

The optimal study of the clinical correlates of more severe withdrawal syndromes would involve a prospective design. Because the present data are retrospective, only minimal information was available on the intensity of past withdrawal episodes as well as their treatments, and the dependence on people's memory might have resulted in an underestimation of the true prevalence of severe withdrawal. On the other hand, the relatively low rate of DTs or convulsions during any specific withdrawal episodes makes such a prospective study difficult. While recognizing the retrospective nature of the data offered here, this investigation does serve several purposes. First, if one assumes that a prior history of DTs or convulsions indicates a heightened probability of future DTs and convulsions, the characteristics offered in Tables 5 and 6 might help clinicians identify those individuals most likely to show severe withdrawal phenomena during a present withdrawal episode. Secondly, the information offers additional data that might be of use to investigators interested in the neurochemical and/or electrophysiological causes of the more severe CNS disturbances associated with alcohol withdrawal.

Of course, the results of this investigation must be interpreted in light of the deficiencies as well as the assets of the work. While the sample size is large, the amount of information that could be gathered about any one withdrawal episode was limited by the retrospective nature of the study. Thus, we were unable to test the potential importance of inadequate treatment of withdrawal episodes in the past as a potential mechanism contributing to the risk for DTs or convulsions. Secondly, a hierarchical regression technique was used here through which we a priori selected specific items for inclusion in a preset order based on our interpretation of the literature. Thus, the relative importance of the various correlates of histories of more intense withdrawal must be carefully interpreted. None the less, the data do indicate that each of the items listed in Tables 5 and 6 appear to add an independent and significant proportion of the variance in explaining histories of more severe withdrawal phenomena.

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