

# Alcohol Misuse and Mood Disorders Following Traumatic Brain Injury

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**Context:** Alcohol abuse and/or dependence (AA/D) and mood disturbance are co-occurring conditions among patients who have had a traumatic brain injury (TBI). However, the relationship between these disorders has not been extensively studied.

**Objective:** To examine the relationship of AA/D and post-TBI mood disorders and the effect of these conditions on psychosocial outcome.

**Design:** Prospective, case-control surveillance study conducted during the first year following trauma.

**Settings:** University hospital level I trauma centers and specialized rehabilitation units.

**Patients:** One hundred fifty-eight TBI patients with closed head injury with and without a history of AA/D.

**Methods:** We prospectively compared psychiatric, neuropsychological, and psychosocial outcomes among the patients, who were evaluated at baseline and at 3, 6, and 12 months after trauma. Psychiatric diagnosis was made using a structured clinical interview and *DSM-IV* criteria. Neuropsychological testing results and quantitative magnetic resonance images were obtained at the 3-month follow-up.

**Results:** A history of AA/D was significantly more frequent among patients who developed mood disorders during the first year following TBI. There was also a significantly higher frequency of mood disorders among patients with alcohol abuse relapse. Patients with a history of AA/D had significantly reduced frontal gray matter volumes than did patients without a history of alcohol abuse. In addition, patients who resumed alcohol abuse had decreased medial frontal gray matter volumes and impaired performance in executive tasks. Both AA/D and mood disorders following TBI were associated with a poor vocational outcome.

**Conclusions:** Previous alcohol abuse increases the risk of developing mood disorders after TBI, and emotional disturbance, in turn, increases the risk of alcohol abuse relapse. Alcohol's neurotoxic effects and TBI likely interact to produce greater disruption of the neural circuits that modulate reward, mood, and executive function. Patients with a history of AA/D who also developed mood disorders following TBI had major difficulties resuming a productive life.

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**A**LCOHOL ABUSE AND/OR DEPENDENCE (AA/D) and mood disturbance are major co-occurring conditions among patients who have sustained a traumatic brain injury (TBI)<sup>1</sup> (hereafter referred to as "TBI patients"). Hibbard et al<sup>2</sup> studied the prevalence of psychopathology in a group of 100 TBI patients approximately 7 years after the traumatic episode. They found that 40% of their patients met *DSM-IV* criteria for AA/D before injury and that 28% were given such diagnoses at the time of the study. A prospective study<sup>3</sup> of 197 TBI patients showed that 42% of them had blood alcohol levels consistent with intoxication at the time of admission to the emer-

gency department and that blood alcohol levels suggested a history of problem drinking. Although alcohol use significantly decreased during the first year after injury, about 25% of the patients reported alcohol-related problems. As expected, preinjury problematic alcohol use predicted alcohol-related problems after TBI.<sup>4</sup>

Kolakowsky-Hayner et al<sup>5,6</sup> compared preinjury and postinjury substance use patterns in patients with TBI and spinal cord injury. The rate of heavy drinking before the injury was high in both groups. Fifty-seven percent of persons with spinal cord injury and 42% of persons with TBI were heavy drinkers. Overall, alcohol use decreased after TBI. However, the authors

concluded that subgroups of patients either abstained or used alcohol frequently.

Alcohol abuse and/or dependence among TBI patients has been evaluated through the use of self-reported alcohol consumption, screening instruments like the Short Michigan Alcoholism Screening Test, measurement of blood alcohol levels at the time of hospital admission, and information retrieved from medical records.<sup>1,3,4,7,8</sup> A composite index that includes most of these measures appears useful for identifying problematic users and for planning appropriate interventions.<sup>9</sup> Alternatively, a specific diagnosis of AA/D can be made using structured psychiatric interviews and *DSM-IV* criteria.<sup>2</sup>

A history of AA/D has been associated with medical complications during acute care of TBI, longer hospital stays, higher mortality rates, and poorer cognitive and psychosocial outcome.<sup>1</sup> The relationship between AA/D and the onset, severity, and course of psychiatric disorders after TBI, however, has not been well characterized. Are patients with AA/D more prone to develop neuropsychiatric complications following TBI? Is this vulnerability related to psychosocial factors, to nonadaptive personality traits, to structural brain changes associated with chronic substance use, or to a complex interaction of these factors? Do mood and anxiety disorders have a role in shaping the patient's compliance with rehabilitation programs or resumption of alcohol abuse? What is the relationship between AA/D, mood disturbance, and a patient's performance in memory and executive function tasks?

In the present study, we prospectively compared psychiatric, neuropsychological, and psychosocial outcomes among TBI patients with and without a history of AA/D during the first year after TBI. We hypothesized that the presence of AA/D would be significantly associated with the development of mood disorders during that 1-year period. In addition, we predicted that, compared with TBI patients without a history of alcohol misuse, TBI patients with AA/D would have measurably poorer cognitive and psychosocial outcomes 12 months after TBI.

## METHODS

### STUDY GROUP

The study group consisted of 158 patients with closed head injury who came from 2 independent samples: the first one was recruited at the University of Maryland R. Adams Cowley Shock Trauma Center, Baltimore (n=66), between 1989 and 1991, and the second was recruited at the University of Iowa Hospitals and Clinics, Iowa City (n=61), or the specialized rehabilitation unit at Iowa Methodist Medical Center, Des Moines (n=31), between 1997 and 2001. Of the 574 patients initially screened for participation in the study, 260 (45.3%) met one or several of the following exclusion criteria: age greater than 80 years, presence of penetrating brain injuries, combined TBI and spinal cord injury, severe communication deficits that precluded a neuropsychiatric evaluation, and severe coexistent medical disorders (eg, congestive heart failure or end-stage renal disease). In addition, 5 patients (0.9%) were excluded because TBI resulted from a confirmed or suspected suicide attempt. Seventy-eight patients (13.6%) were excluded because out-of-state residency status made them unavailable for follow-up. Finally, 73

patients (12.7%) refused to participate in the study. Thus, the 158 patients enrolled in the study represented 27.5% of the patients screened and 51.1% of the patients who met inclusion and exclusion criteria.

The study was approved by the institutional review boards at the hospitals where the patients were enrolled. All patients provided signed informed consent before entering the study. Patients with TBI were evaluated during their hospital admission and at the 3-, 6-, and 12-month follow-up visits.

### SEVERITY OF TBI

The severity of TBI was assessed using the 24-hour Glasgow Coma Scale (GCS)<sup>10</sup> score. Scores between 13 and 15 indicated mild head injury; between 9 and 12, moderate head injury; and between 3 and 8, severe head injury. Patients with a GCS score between 12 and 15 who underwent intracranial surgical procedures or presented with focal lesions greater than 15 cm<sup>3</sup>, however, were considered to have sustained moderate head injury.<sup>11</sup>

### PSYCHIATRIC ASSESSMENT

All patients were assessed by a psychiatrist (R.E.J., S.E.S.) using a semistructured interview, a modified version of the Present State Examination.<sup>12</sup> Patients who were evaluated in Iowa were also assessed using the Structured Clinical Interview for *DSM-IV* diagnoses.<sup>13,14</sup>

A family history of psychiatric disorders was assessed for first-degree relatives on the basis of the family history method using research diagnostic criteria.<sup>15</sup> The Mini-Mental State Examination (MMSE)<sup>16</sup> was used as a global measure of cognitive functioning. Impairment in activities of daily living was assessed using the Johns Hopkins Functioning Inventory, which measures the ability to perform basic and instrumental activities of daily living. Scores range from 0 to 27, with higher scores representing greater impairment. The Johns Hopkins Functioning Inventory has been previously validated in brain-injured populations.<sup>17</sup> Psychosocial adjustment was quantitatively assessed using the Social Functioning Examination and Social Ties Checklist.<sup>18</sup> Initial scores on the Social Ties Checklist assessed social support networks before the traumatic episode. The reliability and validity of each of these instruments have previously been demonstrated in brain-injured populations.<sup>19</sup>

### SUBSTANCE USE ASSESSMENT

A diagnosis of substance abuse or dependence was made according to *DSM-IV* criteria using the information obtained through a structured psychiatric interview (the Structured Clinical Interview for *DSM-IV* diagnoses or Present State Examination), the Social Functioning Examination, and baseline evaluation questionnaires. Information regarding the quantity and patterns of alcohol use was obtained from the patient and from close relatives after the patient's appropriate consent.

### NEUROIMAGING

Computed tomographic images and, occasionally, magnetic resonance images (MRIs) were obtained as part of the standard clinical evaluation in the Emergency and Neurosurgery departments of institutions involved in the study. The nature, extent, and location of traumatic lesions were classified according to Traumatic Coma Data Bank criteria and registered using appropriate Traumatic Coma Data Bank forms.<sup>20</sup> A neurologist trained in the assessment of structural neuroimaging scans (R.E.J.) who was blind to the results of the psychiatric examination read all of the images. In addition, for TBI patients re-

**Table 1. Characteristics of Patients Who Did and Did Not Complete the Study**

Variable	Completers (n = 104)	Dropouts (n = 54)
Age, mean (SD), y*	35.9 (15.7)	28.9 (10.1)
Sex, No. (%) male	71 (68.3)	41 (75.9)
Race, No. (%) white†	96 (92.3)	41 (75.9)
SES, No. (%) in Hollingshead classes IV-V	59 (56.7)	37 (68.5)
Education, mean (SD), y	12.7 (2.4)	12.6 (2.6)
Motor vehicle crash, No. (%)	80 (76.9)	40 (74.1)
GCS score, mean (SD)	11.0 (3.2)	11.1 (3.3)
Moderate to severe TBI, No. (%)	66 (63.4)	32 (59.3)

Abbreviations: GCS, Glasgow Coma Scale; SES, socioeconomic status; TBI, traumatic brain injury.

\* $P = .01$  by Mann-Whitney test.

† $P = .005$  by  $\chi^2$  test.

cruited in Iowa, a research MRI was obtained at the time of the 3-month evaluation using a 1.5T scanner (GE Signa; General Electric, Milwaukee, Wis) at the Radiology Department of The University of Iowa using a standardized protocol.<sup>21</sup> Image analysis was performed using the tools of a locally developed software package (BRAINS-2; Image Processing Laboratory, The University of Iowa) that permits cross-modality image registration, automated tissue classification, automated regional identification, cortical surface generation, volume and surface measurement, 3-dimensional visualization of surfaces, and multiplanar telegraphing. The validity and reproducibility of morphometric analysis using this software have been reported in previous studies.<sup>22-29</sup>

To quantify the gray matter (GM) volume of the frontal lobe, we used an MRI-based parcellation method.<sup>30</sup> This method subdivides the frontal lobe into 11 functionally relevant subregions on the basis of individual gyral and sulcal topography. We grouped the prefrontal areas delimited by our parcellation method into 3 clusters: ventrolateral (ie, lateral orbitofrontal gyri plus inferior frontal gyrus), dorsolateral (ie, superior and middle frontal gyri), and medial (ie, dorsal, rostral, and subcallosal anterior cingulate gyri plus medial orbitofrontal gyri). The interrater reliability for all subregions was calculated with intraclass  $R$  coefficients for cortical GM volume measurements. Intraclass coefficients were high, spanning from 0.86 to 0.99. Morphometric analysis was performed by a research assistant who was extensively trained in this technique and was blind to the psychiatric diagnosis and group assignment of the subjects.

## NEUROPSYCHOLOGICAL EVALUATION

All patients had an MMSE examination at each evaluation. Subjects enrolled in Iowa underwent a neuropsychological assessment that was evaluated by an experienced neuropsychologist (D.M.) at the 3-month and 12-month follow-up visits. The neuropsychological battery included the information, digit span, arithmetic, similarities, digit-symbol, picture completion, and block design subtests of the Wechsler Adult Intelligence Scale-III<sup>31</sup>; the Boston Naming Test<sup>32</sup>; and the Token Test.<sup>33</sup> In addition, the battery focused on memory and frontal-executive functioning, as assessed by the following 8 tests: Rey Auditory Verbal Learning Test (delayed recall trial),<sup>34</sup> Rey Complex Figure Test (delayed recall trial),<sup>34</sup> Trail-Making Test (part A and part B times),<sup>35</sup> Multilingual Aphasia Examination-Controlled Oral Word Association,<sup>36</sup> Stroop Color and Word Test (color/word trial),<sup>37</sup> and Wisconsin Card Sorting Test (number of categories achieved, number of perseverative errors).<sup>38</sup>

## STATISTICAL ANALYSIS

Our comparison of the groups used simple  $\chi^2$  analyses or the Fisher exact test as appropriate. Because some of our continuous measures were not normally distributed, we chose Mann-Whitney tests for comparing the groups. To remain consistent, the Mann-Whitney test was used for all such comparisons. Logistic regression included all of the variables that were significant in univariate tests. A backward-stepwise procedure was used to define the final multivariate model. Neuropsychological and MRI volumetric variables were examined using a version of multivariate analysis of variance based on ranks.

## RESULTS

### TBI GROUP

According to their initial GCS and initial CT data, 98 (62.0%) of the 158 TBI patients had moderate to severe injury and 60 (38.0%) had a mild TBI.

According to the Traumatic Coma Data Bank classification, 92 (58.2%) of the 158 patients had diffuse CT patterns of injury and 66 (41.8%) had focal patterns of injury. The mean and standard deviation of the initial GCS scores were 11.04 and 3.2, respectively. Most of the patients (74.6%) were injured in a motor vehicle crash; the remaining patients were injured as a result of falls (16.5%), assault (4.5%), and other injuries (4.4%).

The TBI patients were evaluated at 3, 6, and 12 months of follow-up. The cumulative attrition rates at 3 and 12 months were 20.6% and 27.2%, respectively, for the Iowa group, and 28.8% and 43.9%, respectively, for patients recruited in Maryland. The difference in attrition is related to methodological differences between the protocols. Patients were followed up at their homes or rehabilitation facilities in Iowa, whereas they were expected to return to the hospital for follow-up in Maryland. Most attrition occurred between the initial evaluation and the 3-month follow-up visit. We compared the demographic and clinical characteristics of the patients who were followed up for 1 year ("completers") with those of the dropouts for each of the groups (**Table 1**). Patients who dropped out were younger than patients who remained in the study (Mann-Whitney  $U = 6.4$ ,  $P = .01$ ), and the proportion of nonwhite patients was significantly higher in the dropout group than in the completers group ( $\chi^2 = 7.8$ ,  $P = .005$ ). Otherwise, there were no significant differences between dropouts and completers with regard to sex, race, socioeconomic status, marital status, or educational level. In addition, there were no significant differences between dropouts and completers with regard to severity of TBI, degree of functional or cognitive impairment, social functioning, or the frequency of psychiatric disorders. History of AA/D was not significantly different for dropouts vs those who were followed up (41.8% vs 31.1%).

### FREQUENCY OF AA/D DURING THE YEAR BEFORE TBI

Of the 158 patients enrolled in the study, 38 (24.1%) were alcohol dependent and 17 (10.8%) abused alcohol. Thus,

**Table 2. Background Characteristics of Patients With and Without AA/D**

Variable	Nondrinkers/ Normal Drinkers (n = 103)	Patients With AA/D (n = 55)
Age, mean (SD), y	34.0 (15.6)	32.6 (12.0)
Sex, No. (%) male*	66 (64.1)	46 (83.6)
Race, No. (%) white	91 (88.3)	46 (83.6)
SES, No. (%) in Hollingshead classes IV-V†	55 (53.4)	41 (74.6)
Education, mean (SD), y‡	13.0 (2.5)	12.1 (2.2)

Abbreviations: AA/D, alcohol abuse and/or dependence;  
SES, socioeconomic status.

\* $P = .01$  by  $\chi^2$  test.

† $P = .009$  by  $\chi^2$  test.

‡ $P = .02$  by Mann-Whitney test.

the frequency of alcohol use disorders during the year previous to the TBI was 34.8%.

### RELATIONSHIP WITH DEMOGRAPHIC VARIABLES

The demographic information of TBI patients with and without AA/D is summarized in **Table 2**. Patients with AA/D were predominantly male ( $\chi^2=6.6$ ,  $P=.01$ ), with fewer years of education (Mann-Whitney  $U=5.3$ ,  $P=.02$ ), and from lower socioeconomic strata ( $\chi^2=6.6$ ,  $P=.009$ ).

### RELATIONSHIP OF AA/D WITH SEVERITY OF TBI AND BASELINE IMPAIRMENT VARIABLES

The effect of premorbid alcohol use disorders on the severity of TBI as well as on impairment variables assessed after resolution of posttraumatic amnesia are summarized in **Table 3**.

There were no significant differences between TBI patients with AA/D and those without with regard to the severity of their injury as assessed by GCS scores. In addition, there were no significant differences between patients with AA/D vs those without with regard to their scores on the MMSE or Johns Hopkins Functioning Inventory. Initial scores on the Social Ties Checklist and Social Functioning Examination were significantly higher (ie, more impaired) in patients with AA/D (Mann-Whitney  $U=9.4$ ,  $P=.002$ , and  $U=14.8$ ,  $P<.001$ , respectively). This suggests that patients with AA/D had poorer premorbid social support networks and poorer social and vocational functioning than did patients without AA/D.

### FREQUENCY OF AA/D DURING THE YEAR FOLLOWING TBI

One-year follow-up data was obtained for 104 (65.8%) of the 158 patients recruited after TBI. Of the 55 patients with AA/D, 30 (55%) completed 1 year of follow-up. Of these, 18 (60%) resumed problematic alcohol use.

We analyzed all of the patients with AA/D who were followed up for 1 year, comparing those who resumed alcohol misuse and those who did not. We found no dif-

**Table 3. Baseline Impairment Variables of Patients With and Without AA/D**

Variable	Nondrinkers/ Normal Drinkers (n = 103)	Patients With AA/D (n = 55)
GCS score, mean (SD)	11.1 (3.2)	10.8 (3.2)
Moderate to severe TBI, No. (%)	64 (62.1)	34 (61.8)
MMSE score, mean (SD)	26.7 (3.7)	27.1 (2.0)
JHFI score, mean (SD)	2.8 (3.7)	2.6 (3.5)
SFE score, mean (SD)*	124 (105)	204 (139)
STC score, mean (SD)†	3.3 (1.7)	4.1 (1.3)

Abbreviations: AA/D, alcohol abuse and/or dependence; GCS, Glasgow Coma Scale; JHFI, Johns Hopkins Functioning Inventory; MMSE, Mini-Mental State Examination; SFE, Social Functioning Examination; STC, Social Ties Checklist; TBI, traumatic brain injury.

\* $P<.001$  by Mann-Whitney test.

† $P = .002$  by Mann-Whitney test.

ferences between the groups with regard to age, sex, socioeconomic status, or the extent and quality of their social network as measured by scores on the Social Functioning Examination and Social Ties Checklist. Patients who relapsed had significantly less education than patients who remain abstinent after discharge (Mann-Whitney  $U=7.1$ ,  $P=.008$ ). In addition, patients who relapsed showed significantly more severe injury as evidenced by lower GCS scores (Mann-Whitney  $U=5.7$ ,  $P=.01$ ) and a greater frequency of moderate and severe injuries than in the abstinent group ( $P=.004$ , Fisher exact test). Patients who resumed alcohol abuse had a significantly higher frequency of focal lesions on their initial CT scans or MRIs ( $P=.008$ , Fisher exact test). There were no significant differences between patients with AA/D who relapsed and those who did not with regard to the frequency of family history of either alcohol addiction or mood disorders.

### RELATIONSHIP OF AA/D WITH MOOD DISORDERS

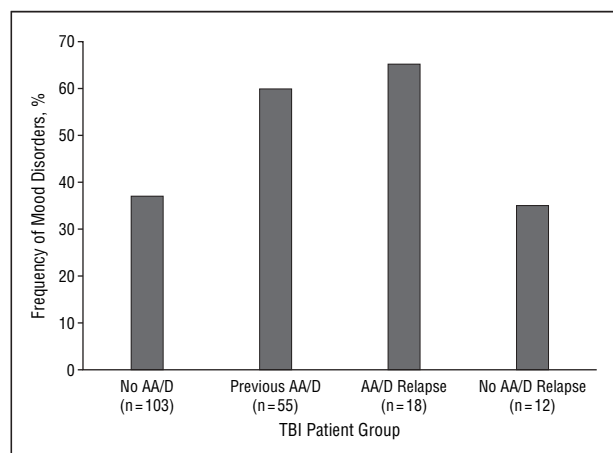
Of the 55 TBI patients with a history AA/D, 33 (60%) developed a mood disorder during the first year of follow-up compared with 38 (36.9%) of 103 patients without a history of AA/D ( $\chi^2=7.8$ ,  $P=.005$ ) (**Figure 1**).

We also found a significant association between AA/D and mood disorders among patients who abused alcohol after their TBI. Of 20 patients with evidence of alcohol abuse in the year after TBI (18 patients who relapsed and 2 incident cases), 15 (75%) developed a mood disorder compared with 37 (44%) of 84 patients who did not abuse alcohol but who developed a mood disorder during this period ( $\chi^2=6.2$ ,  $P=.01$ ).

### RELATIONSHIP WITH NEUROPSYCHOLOGICAL VARIABLES

The MMSE was used as a global measure of cognitive functioning and was the only measure obtained among TBI patients enrolled in Maryland. We did not observe significant differences in MMSE scores between TBI patients with AA/D and those without. Within the Iowa





**Figure 1.** Frequency of mood disorders following traumatic brain injury (TBI). The first 2 columns show the frequency of mood disorders among patients with or without a history of alcohol abuse and/or dependence (AA/D) during the year before TBI. The second 2 columns show the frequency of mood disorders among patients with a history of AA/D who either relapsed or did not relapse into alcohol abuse during the year following TBI.

group, a full neuropsychological evaluation was performed approximately 3 months after posttraumatic amnesia cleared. Although we expected that, after controlling for age and education level, patients with a history of AA/D would show greater cognitive impairment than patients without such a history, this was not supported by our results. We did not find significant differences between the groups in the scores of neuropsychological tests that assessed general intellectual ability, attention, speed of information processing, language, memory, and visuospatial and executive functions.

Of the 18 patients with previous AA/D who were followed up in Iowa, 8 (44%) resumed alcohol abuse during the first year after TBI. We analyzed the effect of alcohol abuse occurring after TBI on the neuropsychological scores obtained at the 1-year follow-up visit. Multivariate analysis of variance showed that, compared with patients who did not abuse alcohol and controlling for age and educational level, patients who resumed alcohol misuse showed impaired cognitive performance in a group of memory and executive tasks (ie, Rey Auditory Verbal Learning Test, Rey Complex Figure Test, Trail-Making Test, Wisconsin Card Sorting Test, and Stroop Color and Word Test) (multivariate analysis of variance, Wilks  $\Lambda$ ,  $F_{4,43}=5.3$ ,  $P<.001$ ). Univariate analysis showed that patients with AA/D were significantly impaired in the interference task of the Stroop test ( $F_1=14.5$ ,  $P<.001$ ) and the delayed recall of the Rey Complex Figure Test ( $F_1=10.7$ ,  $P=.002$ ). However, there were no significant differences in other measures of executive functioning (ie, Wisconsin Card Sorting Test and Trail-Making Test) and a measure of verbal memory (Rey Auditory Verbal Learning Test).

#### RELATIONSHIP WITH STRUCTURAL MRI FINDINGS

We obtained a research MRI for patients recruited in Iowa at the 3-month evaluation. Multivariate analysis of regional GM volumes (ie, frontal medial, frontal dorsolat-

eral, frontal ventrolateral, parietal, and temporal GM), showed that, after controlling for age and severity of brain injury, patients with AA/D showed significantly reduced GM volumes than did TBI patients without AA/D (multivariate analysis of variance, Wilks  $\Lambda$ ,  $F_{3,32}=5.0$ ,  $P=.006$ ). Univariate analysis showed significant differences with regard to total prefrontal medial volumes ( $F_1=9.7$ ,  $P=.003$ ), total prefrontal dorsolateral volumes ( $F_1=4.9$ ,  $P=.03$ ), and total prefrontal ventrolateral volumes ( $F_1=4.8$ ,  $P=.03$ ). However, there were no significant differences between patients with vs those without AA/D with regard to temporal or parietal GM volume.

In addition, multivariate analysis showed that, compared with patients who did not resume alcohol abuse, patients who did had reduced GM volumes (Wilks  $\Lambda$ ,  $F_{3,32}=4.0$ ,  $P=.01$ ). Furthermore, univariate analysis showed that patients who resumed alcohol abuse had significantly reduced total prefrontal medial GM volumes ( $F_1=6.6$ ,  $P=.01$ ). However, there were no significant differences in total prefrontal dorsolateral or total prefrontal ventrolateral GM volume.

#### RELATIONSHIP OF AA/D WITH VOCATIONAL OUTCOME

We used a logistic regression to analyze the effect of a history of AA/D on vocational outcome at the 1-year follow-up evaluation. This was assessed by determining the proportion of patients who were competitively employed or were able to return to their previous occupation at the 1-year follow-up vs those who were not able to achieve these goals.

The regression model included age, severity of brain injury as measured by GCS scores, premorbid social functioning as measured by baseline Social Functioning Examination scores, previous AA/D, the occurrence of mood disorders during the follow-up period, and recruitment site (ie, Iowa or Maryland) as independent variables. The whole-model test was significant (log likelihood,  $\chi^2_6=19.2$ ,  $P=.004$ ). Analysis of the individual variables showed that the occurrence of mood disorders (Wald  $\chi^2_1=4.9$ ,  $P=.03$ ), and a history of AA/D (Wald  $\chi^2_1=4.8$ ,  $P=.03$ ) were associated with poor vocational outcome. Furthermore, 15 (50%) of 30 patients with a history of AA/D returned to their previous occupation or were competitively employed at the 1-year follow-up compared with 58 (78%) of 74 patients without a history of AA/D ( $\chi^2_1=8.2$ ,  $P=.004$ ). Thus, the proportion of patients with AA/D who returned to work was significantly less than that observed in patients without AA/D. Finally, patients with a history of AA/D who also developed mood disorders following TBI had the worst vocational outcome ( $\chi^2_3=15.7$ ,  $P<.001$ ) (**Figure 2**).

#### COMMENT

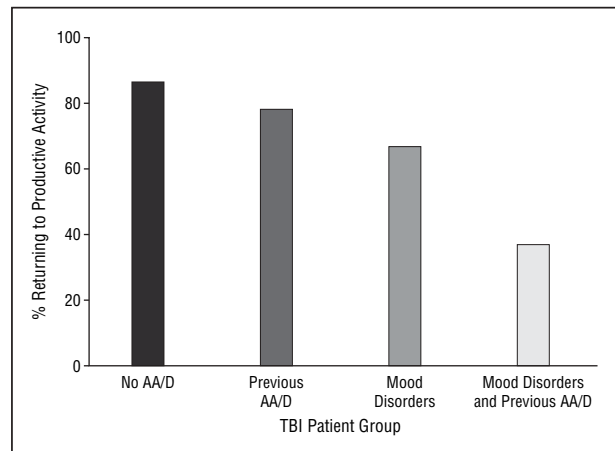
We have studied the relationship between mood and alcohol use disorders among a group of 158 patients with TBI. The frequency of AA/D during the year before trauma was 34.8%. Patients with AA/D were predominantly male, had fewer years of education, and were from lower so-

cioeconomic strata than were TBI patients without a history of alcohol misuse. In addition, patients with AA/D had poorer premorbid social functioning than did TBI patients without a history of AA/D. Mood disorders following TBI were significantly more frequent among patients with a history of AA/D than they were among normal drinkers or nondrinkers.

Sixty percent of patients with a history of AA/D resumed alcohol abuse during the year following TBI. When compared with patients with AA/D who did not relapse, those who did were less educated and had a greater frequency of focal lesions involving the frontal and temporal lobes. In addition, there was a significant association between alcohol abuse during the year following TBI and the occurrence of mood disorders. After controlling for age and the severity of the brain injury, patients with a history of AA/D had lower frontal GM volumes than did TBI patients without a history of AA/D. Furthermore, patients who resumed alcohol abuse during the year following TBI had lower medial frontal GM volumes than did patients without evidence of abuse. Finally, a history of AA/D and the occurrence of mood disorders following TBI were associated with a poor vocational outcome. The group of patients with a history of AA/D who developed mood disorders following TBI had the worst vocational outcome.

We should acknowledge the methodological limitations of our study. The heterogeneity of clinical samples is an important confounder when analyzing the neuropsychiatric complications of TBI. We acknowledge, however, that our conclusions may not pertain to other groups of TBI patients. Although we made a special effort to obtain complete longitudinal data, the attrition rates were high, particularly for the patients recruited in Maryland. However, similar or greater attrition rates are common in the vast majority of longitudinal studies of TBI patients.<sup>39,40</sup> Furthermore, the clinical and demographic characteristics of the patients who dropped out were essentially similar to those of the patients who were followed up. Thus, we have no strong reason to believe that attrition had a significant effect on the main findings. Information about substance abuse was obtained from the patients and their close relatives. We did not confirm substance use through the assessment of randomly obtained biological samples. However, the self-report of alcohol and other drug abuse has been shown to be reliable in TBI populations.<sup>41,42</sup>

Given these limitations, what are the most important implications of the present study? The observed frequency of AA/D before TBI is consistent with the findings of previous investigators.<sup>3,6</sup> Patients with AA/D tended to be young men of lower socioeconomic status. These patients had poor social support networks and impaired social functioning. This might be a consequence of their substance use disorder. However, personality traits such as impulsivity and novelty seeking, and biological factors such as specific polymorphisms in genes related to the regulation of serotonergic and dopaminergic systems, might affect both social behavior and the occurrence of substance use disorders. Genetic vulnerability may interact with adverse environmental influences (eg, abnormal attachment experiences, emotional and physi-



**Figure 2.** Relationship of mood and alcohol use disorders with vocational outcome. Patients with a history of alcohol abuse and/or dependence (AA/D) who developed mood disorders during the year following traumatic brain injury (TBI) were least likely to resume a productive life ( $P < .001$ ).

cal abuse, or social exclusion) to impair social integration and to increase the risk of AA/D.<sup>43-53</sup>

Patients with a history of AA/D had a greater frequency of mood disorders during the year following TBI than did TBI patients who were normal drinkers or nondrinkers. There is a significant degree of overlap between the structures and circuits involved in addiction and the circuits that regulate emotion and mood,<sup>54-58</sup> and there is evidence that these neural circuits can be disrupted by the effects of chronic alcohol abuse. It is also likely that alcohol's toxic effects and TBI interact to produce more severe structural brain damage and more profound changes in the ascending aminergic pathways that modulate reward, mood, and executive function.<sup>43,59-64</sup> The finding that patients with a history of AA/D had significantly decreased frontal GM volumes compared with TBI patients without such a history is consistent with this hypothesis.

Patients who resumed alcohol abuse after TBI were not different from patients who did not relapse with regard to the degree of functional impairment, the quality of their social support network, or their previous social and vocational functioning. In addition, there were no significant differences between patients who relapsed and those who did not in the frequency of family history of mood or addictive disorders. Patients who relapsed, however, had a greater frequency of focal brain lesions (ie, contusions and extracranial hemorrhages), preferentially involving the prefrontal cortices and the anterior temporal lobes. These structures form part of the neural circuits that mediate critical aspects of addictive behavior such as stimulus salience attribution, reward expectation, and response inhibition.<sup>60,65</sup> Furthermore, patients who abused alcohol during the year after TBI showed impaired performance on the interference task of the Stroop Color and Word Test and had reduced medial frontal GM volumes suggestive of abnormal functioning of the anterior cingulate and prefrontal medial cortices, which are regions of the brain involved in conflict monitoring, error detection, decision making, and reward mechanisms.<sup>66-74</sup> Taken together, the selective involvement of prefrontal cortex and anterior temporal lobes

in TBI and the abnormal behavioral regulation that results from these lesions can increase the risk of relapse among patients with a history of alcohol abuse.

Alcohol abuse during the follow-up period was also significantly associated with the occurrence of mood disorders. It is difficult to ascertain whether mood disturbance was the cause or the effect of alcohol abuse. In addition, the relationship between alcohol abuse and mood disorders is reciprocal, with alcohol-related brain changes producing dysphoria and mood disturbance that perpetuate alcohol abuse.

A return to productive activity is probably the most relevant outcome for survivors of TBI.<sup>75-80</sup> In our study, patients with a history of AA/D who also developed mood disorders following TBI were those least likely to resume a meaningful, productive, and independent life. These are probably the patients with the most severe disturbances in behavioral and emotional control, social cognition, insight, and problem-solving ability. Substance abuse rehabilitation programs and psychopharmacologic treatment need to be adapted to the special needs and particular deficits of this group of patients to improve their prognosis.

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