Familial Psychiatric Illness and Posttraumatic Stress Disorder: Findings From a Family Study of Substance Abuse and Anxiety Disorders

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Background: Aside from the possibility of a direct relationship between individual and familial posttraumatic stress disorder (PTSD), there is accumulating evidence that implicates a family history of psychiatric and substance use disorders as an important risk factor in the development of PTSD and associated symptoms.

Method: The familial risk of DSM-III-R PTSD was examined within a family study of clinical- and community-ascertained probands (N = 263) and their 1206 adult first-degree relatives.

Results: Although PTSD among probands was not found to significantly elevate the risk of PTSD among first-degree relatives, an elevated rate of PTSD was found among the relatives of drug abusing probands compared with the relatives of probands with alcoholism, other anxiety disorders, and normal controls. Additionally, affective disorders were significantly associated with PTSD in relatives ($p < .01$). When these familial and individual associations were examined according to gender, drug disorders in probands were significantly associated with PTSD only among male relatives ($p < .01$), while the association between PTSD and comorbid affective disorders was seen primarily among female relatives ($p < .01$).

Conclusion: Although probands in the present family study were not selected specifically for PTSD, the data afforded a unique opportunity to examine the profile of familial psychopathology as a part of the complex picture of susceptibility for PTSD. Future family study research will be able to determine the generalizability of the present findings through more complete measurement of diverse forms of trauma.

(J Clin Psychiatry 2001;62:715–720)

Received October 11, 2000; accepted June 7, 2001. From the Department of Psychology, Wesleyan University, Middletown (Dr. Dierker); and the Departments of Epidemiology and Public Health, Psychiatry, and Psychology, Yale University School of Medicine, New Haven, Conn. (Dr. Merikangas).

Supported in part by grants AA07080, AA09978, DA05348, DA09055, and MH30929 and Research Scientist Development Awards K02-MH00499 and DA 00293 from the Alcohol, Drug Abuse, and Mental Health Administration of the United States Public Health Service, Bethesda, Md. (Dr. Merikangas).

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Dierker and Merikangas have no significant commercial relationships to disclose relative to the presentation.

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The American Psychiatric Association first defined specific symptom criteria associated with posttraumatic stress disorder (PTSD) in DSM-III.[1] Since that time, a few studies have examined both the specific and general role that an individual's family history may play in the development of PTSD. The evidence available to date supports some elevation in the rates of this disorder and, more generally, posttraumatic symptoms among relatives of PTSD probands. A recent twin study,[2] for example, found genetic factors to account for a moderate proportion of the risk for PTSD symptoms from each of the criteria clusters: reexperiencing (13%–30%), avoidance (30%–34%), and arousal (28%–32%). Similarly, a twin study conducted by Skre and colleagues[3] showed that PTSD was significantly more prevalent in monozygotic than in dizygotic cotwins. Furthermore, Famularo and colleagues[4] showed PTSD rates to be significantly elevated among children of mothers with PTSD drawn from a family court system. In contrast to these findings, Davidson and colleagues[5] failed to detect increased rates of PTSD among family members of female rape victims with PTSD.

Aside from the possibility of a direct relationship between individual and familial PTSD, there is also accumulating evidence that implicates a family history of psychiatric and substance use disorders as important risk factors in the development of PTSD and associated symptoms.[6–9] In a study of young adults drawn from a health mainte-

nance organization, familial anxiety was found to be associated with a diagnosis of PTSD.[10] Similarly, Davidson and colleagues[6] found anxiety to be more common among relatives of PTSD subjects compared with those of depressed subjects. A more recent family study by Davidson and colleagues[5] employing direct interview techniques found that, compared with other disorders among family members, familial affective disorders were most strongly associated with PTSD among probands. While alcohol and drug use disorders have been shown to be more common among relatives of PTSD subjects compared with relatives of subjects with depression or generalized anxiety disorder,[6] the familial association between PTSD and substance abuse/dependence has not been consistently replicated.[5] Furthermore, few studies have examined the independent contribution of disorder related to the abuse or dependence of different types of substances.

Based on the evidence regarding the association between PTSD and a family history of anxiety and substance use disorders, the familial risk for PTSD was examined in a family study designed to investigate the association between substance and anxiety disorders.[11,12] The major goals of the family study were to examine the patterns of familial aggregation of substance and anxiety disorders, to assess patterns of comorbidity in relatives, and to test mechanisms of comorbidity through evaluation of the patterns of transmission and cross-transmission of anxiety and substance abuse in families.[11,12] Although probands were not specifically selected on the basis of having PTSD, this sample provides a unique opportunity to examine specific associations among familial disorders in a sample that may be at particularly high risk for PTSD.

One of the chief limitations to the study of the familial risk factors for PTSD is the prerequisite of exposure to a traumatic stressor for its development. Relatives without such exposure would therefore not be at risk for the development of PTSD. Appropriate analyses require evaluation of familiality conditional on such exposure. In an attempt to further elucidate familial risk, the present analyses also took into account the disorders most strongly associated with PTSD (drug abuse/dependence, alcoholism, anxiety, and depression). Because the presence of psychiatric and substance abuse comorbidity has been consistently established[10,13–18] and may in turn greatly influence the risk status of individual family members, the present analyses included an examination of lifetime comorbidity. The following questions were addressed: (1) Are psychiatric and substance use disorders associated with exposure to trauma in probands and relatives? (2) Does PTSD among index cases selected for substance and anxiety disorders increase the risk of PTSD among first-degree relatives? (3) Is the presence of anxiety and substance use disorders among index cases associated with higher rates of PTSD among their first-degree relatives? and (4) Are significant patterns of familial aggregation sex-specific?

METHOD

Sample and Diagnostic Procedures

All procedures complied with strict ethical standards in the treatment of human subjects. Care was taken in the informed consent process to assure that participants were knowledgeable about the study and willing to participate. A total of 263 probands were selected from a community mental health center or through a random digit dialing procedure in the community for marijuana/sedative abuse, alcoholism, and/or anxiety disorders. All of the normal controls and 30% of the psychiatric cases were recruited through the random digit dialing procedure. The remaining psychiatric cases were recruited from the mental health center. Probands were assigned to 1 of 4 hierarchical lifetime diagnostic groupings. Groups of probands consisted of 36 probands diagnosed with drug use disorders including anxiolytic, sedative, or benzodiazepine abuse or marijuana abuse or dependence; 89 probands with a diagnosis of alcohol abuse/dependence; 77 probands with an anxiety diagnosis; and 61 normal controls with no history of an Axis I disorder. Probands were assigned to the drug group if their history of drug abuse or dependence overshadowed any history of alcoholism. Assignment to this cell was based on a blind and independent review by clinicians with extensive experience in the evaluation and treatment of substance abuse. For subjects with a lifetime history of abuse or dependence of multiple drugs, predominant substance of abuse was determined through review of a life chart and the following information from the diagnostic interview, treatment records, when relevant, and family history: age at onset, order of onset, quantity, frequency, chronicity, substance of choice, number of symptoms, and severity. Other drugs included stimulants other than cocaine (e.g., amphetamines) and tranquilizers (e.g., diazepam, alprazolam), but use of these drugs was not found to be predominant in any of the probands in the present study. Assignment to the anxiety group was based on the presence of either panic disorder or social phobia in the absence of substance-related disorders. Comorbid disorders including major depression, dysthymia, bipolar disorder, and PTSD were present among cases in each of the diagnostic groups except for normal controls.

Through random digit dialing procedures, the normal controls were recruited from the same general population as the affected probands and administered the same protocol. On the basis of review by clinicians with expertise in substance abuse, probands from the clinic or community were excluded from the study if there was evidence of extensive organic mental impairment, schizoaffective disorder, schizophrenia, or a substantial history of drug dependence, particularly intravenous drug use. The rationale for including a combination of clinically referred probands and probands recruited at random from the community was to minimize bias associated with treatment seeking.

Table 1. Rates of Trauma and PTSD Diagnoses Among Probands and Interviewed Relatives[a]

PTSD Diagnosis/ Exposure to Trauma	Proband Diagnostic Group				
	Drug (N = 36)	Alcohol (N = 89)	Anxiety (N = 77)	Control[b] (N = 61)	p Value
Probands					
Traumatic stressor, %	36[A]	34[A]	18[B]	10[C]	< .01
PTSD, %	22[A]	15[A]	5[B]	0[C]	< .05
Relatives					
No. of relatives	30	88	73	70	
Traumatic stressor, %	17	22	10	19	NS
PTSD, %	17[A]	2[B]	1[B]	7[B]	< .01

[a]Abbreviation: PTSD = posttraumatic stress disorder.
[b]Controls were selected if free from psychiatric diagnoses including PTSD. Different capital letter superscripts demonstrate significant differences between rates within each row.

All adult first-degree relatives were approached for direct interview by an interviewer blind to the proband diagnoses. The diagnostic interview was a modified version of the DSM-III-R semistructured Schedule for Affective Disorders and Schizophrenia, current and lifetime versions.[19] Approximately equal proportions of relatives were interviewed across proband groups. Sixty-five percent of the relatives whom probands gave consent to contact were interviewed directly. For all first-degree relatives who were not interviewed directly, the proband and interviewed first-degree relatives provided family history using a version of the Family History-Research Diagnostic Criteria developed by Andreasen and colleagues[20] for data collected by the family history method and adapted to DSM-III and DSM-III-R criteria. The final diagnoses were "best-estimate" diagnoses based on all available information, including the diagnostic interview (when available), family history reports on each proband and relative, and medical records. Interview status was controlled in all analytic models.

The evaluation of PTSD included the gate question "Did you ever have a traumatic experience?" This was followed by examples of traumatic events including a serious accident, plane crash, active combat or terrorist bombing, natural disaster, home burning down, or other. PTSD symptom questions were asked if the respondent endorsed having experienced any sort of trauma similar to the examples given.

Data Analysis

Data analysis included standard chi-square tests for n-way tables of categorical level variables and analyses of variance for continuous outcomes. The multiway contingency tables for the association between diagnoses and stressors in probands and relatives were analyzed via logistic regression. The main effect of the following variables on both traumatic stress and a diagnosis of PTSD in relatives was examined: (1) PTSD in probands; (2) comorbid drug use disorders, alcoholism, other anxiety disorders, and affective disorder in probands; (3) sex of proband; (4) age of proband (continuous); (5) presence of comorbid disorders in relatives (drug disorders, alcoholism, other anxiety disorders, and affective disorders); (6) sex of relative; (7) age of relative (continuous); and (8) interview status of relative (direct interview vs. family history information). Because PTSD was not a selected disorder among probands and rates were low relative to the selected disorders, interaction terms related to PTSD were not included in the model.

RESULTS

Trauma Exposure and PTSD by Proband Group

Demographic characteristics of the probands are presented in previous publications.[11,12,21] In brief, the probands were white men (50%) and women (50%) ranging in age from 24 to 56 years (mean ± SD age = 40 ± 6.1 years) from socioeconomically diverse backgrounds. Not surprisingly, there were substantially more women in the anxiety group (74%) and substantially more men in the alcohol abuse/dependence group (29%). The remaining proband groups were similar in terms of gender.

Table 1 presents the rates of trauma and PTSD diagnoses among probands and interviewed relatives. An initial examination of the key diagnostic gate question regarding PTSD in the interview ("Did you ever have a traumatic experience?") revealed that exposure to a stressor was more prevalent among probands selected for drug and alcohol abuse/dependence compared with both the anxiety and control probands (see Table 1). Anxiety probands reported rates of trauma between those of substance abusers and controls. In contrast, no significant differences were found among interviewed relatives for rates of traumatic exposure by proband group.

Of the probands and relatives endorsing exposure to a traumatic event, a smaller proportion was found to meet diagnostic criteria for PTSD. Chi-square and Fisher exact analyses revealed a significantly elevated rate of PTSD among drug- and alcohol-abusing probands compared with anxiety probands and normal controls. Among interviewed relatives, the rate of PTSD was elevated among relatives of drug abusers compared with each of the psychiatric groups and controls.

Correlates of PTSD in First-Degree Relatives

To more thoroughly examine the familial aggregation and comorbidity associated with PTSD while controlling for potential confounders such as sex, age, and interview status, logistic regression models were employed to investigate the association between PTSD in probands and relatives. Sex-specific analyses were also conducted. Results revealed that PTSD in the proband did not significantly increase the risk of PTSD in the relatives, although the

Table 2. Association Between PTSD and Other Psychiatric Disorders Among Probands and Relatives[a]

Diagnosis	PTSD in Relatives: Adjusted Odds Ratio (95% Confidence Interval)		
	Women[b] (N = 603)	Men[b] (N = 603)	All[c] (N = 1206)
Disorders in probands			
PTSD vs no PTSD	3.8 (0.58 to 25.62)	1.2 (0.12 to 12.41)	2.1 (0.52 to 8.18)
Drug disorder vs no drug disorder	3.2 (0.59 to 16.95)	7.7* (1.40 to 42.89)	3.8* (1.25 to 11.59)
Alcohol disorder vs no alcohol disorder	1.3 (0.26 to 6.54)	2.2 (0.33 to 14.84)	1.4 (0.43 to 4.30)
Anxiety vs no anxiety	0.4 (0.10 to 1.89)	0.2 (0.04 to 1.29)	0.4 (0.15 to 1.17)
Affective disorder vs no affective disorder	0.7 (0.13 to 3.68)	0.8 (0.13 to 5.06)	0.8 (0.26 to 2.73)
Comorbid disorders in relatives			
Drug disorder vs no drug disorder	3.3 (0.63 to 16.83)	0.5 (0.03 to 6.80)	1.4 (0.38 to 5.35)
Alcohol disorder vs no alcohol disorder	0.2 (0.02 to 2.00)	0.8 (0.16 to 4.23)	0.5 (0.15 to 1.88)
Anxiety vs no anxiety	1.6 (0.40 to 6.17)	3.1 (0.69 to 13.93)	2.0 (0.75 to 5.30)
Affective disorder vs no affective disorder	21.8* (2.39 to 198.97)	3.2 (0.63 to 16.05)	5.9* (1.98 to 17.34)

[a]Abbreviation: PTSD = posttraumatic stress disorder.
[b]Adjusted for interview status, age of the relative, and age and sex of the proband.
[c]Adjusted for interview status, age and sex of the relative, and age and sex of the proband.
*$p < .01$.

odds ratio (OR) was approximately 2. Drug use disorders in probands (including anxiolytic, sedative, or benzodiazepine abuse or marijuana abuse or dependence), however, were significantly associated with PTSD in relatives (OR = 3.8). When other proband disorders as well as comorbid disorders in relatives were considered, a significant association was found between the affective disorders in relatives and PTSD. Whereas proband affective disorders did not predict PTSD in relatives, comorbid affective disorders in the relatives were associated with an increased risk of PTSD (Table 2).

When PTSD was examined by sex of relative, the significant associations were found to be both stronger and sex-specific. The significant association between drug use disorders in probands and PTSD in relatives was found to be limited to male relatives (OR = 7.7), while the association between PTSD and comorbid affective disorders was limited to female relatives (OR = 21.8).

DISCUSSION

Although probands in the present family study were not selected specifically on the basis of having PTSD, the data afforded a unique opportunity to examine specific associations within a sample that is at high risk for PTSD. Whether the associations based on the present analyses can be generalized to untreated samples or to samples seeking treatment for PTSD, depression, or other forms of psychiatric disturbance will require confirmation in future analyses based on diverse family study designs. Presently, the familial risk of PTSD and the interrelated associations with psychiatric comorbidity represent a relatively understudied area of research.

The present findings demonstrated that the rate of PTSD was significantly elevated among the drug-abusing probands and their relatives. Most notably, after controlling for comorbid psychopathology (including alcoholism), a nearly 4-fold increase in risk for PTSD was found among the relatives of probands selected for the study based on a current or lifetime diagnosis of anxiolytic, sedative, or benzodiazepine abuse or marijuana abuse or dependence. Analyses conducted by gender of the relative further revealed that this association was specific to men. Notably, although self-reported exposure to a trauma was found to be more common among drug-abusing probands than among other probands, differential exposure was not found to drive the familial association. That is, no difference was found for trauma exposure between groups of relatives based on the diagnostic status of the probands. This suggests that, although they are no more susceptible to traumatic experiences, the relatives of drug-abusing probands are more susceptible than those not related to drug-abusing probands to the development of PTSD given exposure to trauma.

In contrast to the positive drug abuse/dependence findings, anxiety among probands was not associated with PTSD among relatives, a result that is contrary to previous work based on a community sample.[10] To examine this association further, post hoc analyses were conducted that attempted to better reproduce the methods used in previous investigations. Specifically, we replicated our models with those subjects whose diagnoses were derived exclusively from family history reports. These analyses also failed to demonstrate an association between proband anxiety and PTSD among relatives, quite likely a result of the present clinic sampling, which may have yielded subjects with more severe psychiatric conditions and types of traumatic exposure.

With respect to comorbidity, the present analyses confirmed earlier findings in that affective disorders, rather than anxiety disorders, were significantly associated with PTSD.[10,17,18] Again, when analyses were conducted by gender, the association was found to be sex-specific, this time limited to female relatives. Notably, our findings did

not demonstrate a significant association between anxiety disorders and PTSD once the presence of other forms of psychopathology were controlled. These findings confirm those of the National Comorbidity Survey, which showed that affective disorders were the only form of psychiatric disorder significantly associated with PTSD.[18]

Possible mechanisms responsible for the relationship between PTSD and the affective disorders include (1) shared genetic or environmental risk factors and (2) a causal link between the 2 conditions.[22] The present study found support for neither mechanism. Based on reported age at onset for both PTSD and affective disorders, patterns in order of onset were mixed, possibly suggesting shared etiology. However, the lack of significant cross-aggregation between proband affective disorders and PTSD in relatives failed to support this hypothesis. A third explanation for PTSD/depression comorbidity is that the expression of depression in individuals with PTSD may in fact represent periods of subclinical PTSD. Earlier studies have highlighted the fact that several DSM criteria C and D symptoms of PTSD (e.g., diminished interest, restricted range of affect, sleep difficulties, difficulty concentrating) are also among the symptoms of major depression.[16] The possibility remains that, although individuals with PTSD commonly meet criteria for major depression, these symptoms may be distinct from similar symptoms expressed among patients without PTSD. The mechanisms surrounding the association between comorbid PTSD and affective disorders remain an important area of inquiry.

The present findings should be considered within the context of study limitations. First, while rates of PTSD among psychiatric probands were found to be elevated compared with those previously reported in general population surveys,[10,14,16] particularly among drug-abusing probands, corresponding rates of PTSD among first-degree relatives were surprisingly low (i.e., from 1% to 17%). This low rate is quite likely due to the format of the gate question, which used a limited number of examples of traumatic events (i.e., serious accident, plane crash, active combat or terrorist bombing, natural disaster, home burning down, or other) and did not include physical or sexual abuse, rape, and other types of victimization commonly found to trigger posttraumatic stress. This narrow list quite likely caused an underestimation of trauma exposure and PTSD symptoms in both probands and relatives. Second, earlier studies have established the importance of the type and severity of traumatic event in the development of PTSD.[23] Given that the trauma type and severity were not established in the present study, these characteristics could not be used to interpret the generalizability of the present findings. Family study research based on the more careful articulation of posttraumatic phenomenology is greatly needed.

Several notable strengths also characterize the present study. These include (1) the use of direct interview techniques to investigate the familial nature of PTSD,[5] (2) a sufficient number of both male and female probands and relatives that allowed for the investigation of sex differences in comorbidity and PTSD, (3) the use of multivariate models controlling for interrelationships among comorbid psychopathology and other potential confounders, and (4) the ascertainment of probands from both clinic and community settings, enhancing the generalizability of study results by minimizing potential selection biases inherent in most family studies derived from nonrepresentative samples.

When interpreting family study results, it is important to remember that, while moderate heritability estimates can be established for PTSD or its component symptoms, the expression of the disorder is quite likely the result of complex interactions among genetic and environmental factors.[2] To date, the possible heterogeneity of the illness in terms of presenting subtypes, complex comorbidities, and changes over time and context remains unresolved.[24] Furthermore, the influence of gender in terms of risk of traumatic events, type of trauma experienced,[25] and a host of intervening individual and biological factors highlights the challenges faced in future research. The careful mapping of etiologic pathways and accurate prediction of course will have significant implications for the prevention and treatment of posttraumatic stress. This work will necessarily require the cross-informing of findings based on twin and family study research, pharmacotherapy outcome trials, and longitudinal investigations drawn from both epidemiologic samples and diverse treatment populations.

Analyses conducted on the familial transmission of PTSD within a study designed to investigate the relationship between substance use disorders and anxiety disorders have provided a unique opportunity to study the familial and comorbid relationships between PTSD and a broad range of psychiatric disorders. Although the current analysis found no evidence of familial aggregation of PTSD, the results confirm earlier findings that a family history of psychiatric disorder increases risk for PTSD among relatives and extend those findings to suggest that drug use disorders other than alcoholism represent a strong familial association. The present results add to the accumulating evidence that a specific profile of familial psychopathology may be established as a part of the complex picture of susceptibility for PTSD. Future work on the offspring of these probands will help elucidate mechanisms for comorbidity of other psychiatric disorders and PTSD.

Drug names: alprazolam (Xanax and others), diazepam (Valium and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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