

Posttraumatic Stress Disorder and Drug Disorders

Testing Causal Pathways

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Background: Although there is a high degree of comorbidity between posttraumatic stress disorder (PTSD) and drug use disorders, little is known about causal relationships between PTSD, exposure to traumatic events, and drug use disorders.

Methods: In a longitudinal study in southeast Michigan, 1007 adults aged 21 to 30 years were initially assessed in 1989 and were followed up 3 and 5 years later, in 1992 and 1994. Psychiatric disorders according to *DSM-III-R* criteria were measured by the National Institute of Mental Health Diagnostic Interview Schedule. To take into account temporal sequencing, the associations between PTSD, traumatic events, and drug use disorders were analyzed by using Cox proportional hazards models with time-dependent covariates.

Results: Posttraumatic stress disorder signaled an increased risk of drug abuse or dependence (hazards

ratio, 4.5; 95% confidence interval, 2.6-7.6, adjusted for sex), whereas exposure to traumatic events in the absence of PTSD did not increase the risk of drug abuse or dependence. The risk for abuse or dependence was the highest for prescribed psychoactive drugs (hazards ratio, 13.0; 95% confidence interval, 5.3-32.0). There was no evidence that preexisting drug abuse or dependence increased the risk of subsequent exposure to traumatic events or the risk of PTSD after traumatic exposure.

Conclusion: The results suggest that drug abuse or dependence in persons with PTSD might be the inadvertent result of efforts to medicate symptoms, although the possibility of shared vulnerability to PTSD and drug use disorders cannot be ruled out.

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POSTTRAUMATIC STRESS disorder (PTSD) is highly comorbid with other psychiatric disorders, including drug dependence.¹⁻¹¹ Studies of Vietnam veterans provided the initial evidence of the comorbidity between PTSD and drug use disorders.^{8,12-16} Breslau et al¹ previously reported evidence of this comorbidity in a community sample of young adults, a finding that has been confirmed in other epidemiological studies.^{2,17} However, little is known about the causal pathways that might explain the observed comorbidity.

Several explanations of the relationship between PTSD and drug use disorders have been proposed. Based largely on clinical observations, the self-medication explanation hypothesizes that psychoactive substances are used to relieve traumatic memories and other painful symptoms of PTSD.^{18,19} Alternatively, illicit drug use can increase the risk of PTSD through 2 potential mechanisms. First, persons who use drugs might be more likely to be in-

involved in so-called high-risk behaviors, which increase their risk for experiencing a traumatic event that could lead to PTSD.^{17,19} Second, drug users might be more susceptible to PTSD after traumatic exposure. They also might have experienced changes in brain neurochemical systems that increase their susceptibility to psychiatric symptoms.¹⁹ On the other hand, the relationship between PTSD and drug use disorders might be noncausal. For example, antisocial personality and conduct disorder and major depression have been linked to traumatic exposure, PTSD, and drug use disorders.^{1,3,5,6,17,20-22} These disorders might predispose persons to substance abuse and PTSD, accounting for the observed association between PTSD and drug use disorder.

To test potential causal pathways between PTSD and substance use disorders, we analyzed data from a longitudinal study of young adults. The following questions were addressed: (1) Does PTSD increase the risk of subsequent drug use disorder? (2) Does preexisting

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RESPONDENTS AND METHODS

RESPONDENTS AND DATA

Data were collected on a randomly selected sample from the membership list of a 400 000-member health maintenance organization in southeast Michigan. Of the 1200 members aged 21 to 30 years randomly selected at the initial wave of data collection in 1989, 1007 (83.9%) participated. Follow-up interviews were conducted in 1992 and 1994 in which 979 (97.2%) and 971 (96.4%) respondents completed interviews, respectively. On key characteristics, the study sample was representative of the geographic area, with some underrepresentation of the extremes of the socioeconomic distribution (**Table 1**). Information on the sample and the population appears elsewhere.¹

The National Institute of Mental Health Diagnostic Interview Schedule-Revised (DIS)²⁴ was used to gather information on the history of psychiatric disorders based on *DSM-III-R*.²⁵ The baseline interview obtained data on the lifetime history of psychiatric disorders, and follow-up interviews obtained data on the psychiatric symptoms and disorders occurring in each of the subsequent intervals. Interviews were administered in person by trained lay interviewers.

DEFINITIONS OF PTSD AND DRUG ABUSE OR DEPENDENCE

The diagnosis of PTSD in *DSM-III-R* requires the presence of a qualifying traumatic event and criterion symptoms related to the event, which include reexperiencing, avoidance or numbing, and increased arousal. For an event to qualify as a stressor, it must be "outside the range of usual human experience" and "markedly distressing to almost anyone."²⁵ The DIS lists typical PTSD events, using the examples from the *DSM-III-R* and asks respondents whether they have ever experienced an event of that type. If a reported event does not fit the definition of a stressor, it is excluded from further inquiry, and respondents are asked whether they have experienced any other traumatic events. Beginning with the worst event, the DIS inquires about PTSD symptoms associated with up to 3 events at each wave of interviews.

Drug abuse or dependence (A/D) was determined according to *DSM-III-R* criteria for the following classes of drugs used on one's own to get high: stimulants, sedatives or tranquilizers, marijuana, cocaine, heroin or other opiates, and hallucinogens. *Drug dependence* is defined as the presence of 3 or more symptoms from a list of 9 dependence symptoms encompassing cognitive, behavioral, or physiological problems that characterize compulsive drug use. *Drug abuse* is a residual category, defined by continued use despite knowledge of health, psychological, or social problems caused by the substance or recurrent use in situations in which use is hazardous.

A diagnosis of prescribed psychoactive drug A/D was based on symptoms due to 1 of 2 types of drug use: (1) extramedical use (eg, used on one's own to get high) of 3 categories of drugs that often are prescribed: stimulants (eg, amphetamines), sedatives or tranquilizers (eg, barbiturates, sleeping pills, Seconal, Valium, Librium, Quaalude, Xanax), and opiates other than heroin (eg, codeine,

Demerol, morphine, Percodan, methadone, Darvon, and Dilaudid); and (2) use as prescribed of a "tranquilizer, sedative, pain pill, antidepressant, or headache medicine" every day for 2 weeks or more. The second type of prescribed psychoactive drug A/D defines persons who became dependent despite adherence to medical instructions. Respondents were probed about specific drugs that were prescribed, confirming that the prescribed medications were psychoactive drugs.

STATISTICAL ANALYSIS

The age of onset of drug A/D, PTSD, and traumatic exposure were determined by using the combined retrospective and prospective data from the 3 interviews. For PTSD and drug use, the age of onset was defined as the earliest onset of a symptom among those meeting criteria for the disorder. The Cox proportional hazards models with time-dependent covariates was used.^{26,27} Hazards ratios from Cox proportional hazards models provide estimates of the risk of an outcome for those with vs those without a specified risk factor. Chronological age was used as the indicator of time, and data from respondents not experiencing the specified outcome by the time of the final interview were censored. In cases in which the outcome and time-dependent covariate occurred during the same year, it was impossible to determine which came first. To avoid imposing a temporal sequence based on a priori assumptions, observations with tied onset times were censored just before the year in which the tie occurred.⁶ Cox proportional hazards models were fit using the proportional hazards procedure in SAS statistical software (PHREG procedure).²⁸

Three sets of Cox proportional hazards models were used. The first set of models addressed question 1, estimating the relative hazard of drug A/D in relation to previous exposure to a traumatic event and PTSD. In these models, traumatic exposure was coded as present (1) at the age of first exposure and subsequent ages. If PTSD occurred after traumatic exposure, PTSD was coded as present (1) at that age and subsequent ages. To account for depression as a possible confounder, we used 3 time-dependent covariates: depression without previous PTSD, PTSD without previous depression, and PTSD with previous depression. Persons with neither depression nor PTSD served as the reference category. Hazards ratios were estimated in the following proportional hazards model:

$$h_i(t) = h_0(t)e^{\alpha X_i(t) + \beta Y_i(t) + \gamma Z_i(t)}$$

where $h_i(t)$ is the expected hazard for individual i at time t ; $X_i(t) = 1$ if the most recent event before time t was depression with no history of PTSD, otherwise $X_i(t) = 0$; $Y_i(t) = 1$ if the most recent event before time t was PTSD with no history of depression, otherwise $Y_i(t) = 0$; and $Z_i(t) = 1$ if the most recent event before time t was PTSD with a history of depression, otherwise $Z_i(t) = 0$. The coefficients, α , β , and γ represent the risk associated with depression alone, PTSD alone (or with subsequent depression), and PTSD with preexisting depression, respectively, relative to those with neither of these disorders.

To address question 2, a second set of models estimated the hazards of exposure to a traumatic event in relation to preexisting drug A/D. Question 3 was addressed in models that estimated the relative hazards of PTSD by preexisting drug A/D, using the subset of 540 respondents who reported exposure to a qualifying stressor.

Table 1. Sample Characteristics (N = 1007)

Characteristic	No. (%)
Sex	
Male	386 (38.3)
Female	621 (61.7)
Education	
Less than high school	37 (3.7)
Completed high school	212 (21.0)
More than high school	462 (45.9)
Completed college	296 (29.4)
Race	
White	813 (80.7)
Black	194 (19.3)
Marital status	
Married	451 (44.8)
Separated or divorced	54 (5.4)
Never married	502 (49.9)
Family income, \$*	
<20 000	193 (19.6)
20 000-39 999	379 (38.6)
40 000-59 999	254 (25.8)
≥60 000	157 (16.0)

*Data not provided by 24 respondents.

drug use disorder increase the risk of subsequent exposure to traumatic events? (3) Does preexisting drug use disorder increase the risk of PTSD after a traumatic event? We controlled for preexisting major depression and early conduct problems, because these factors have been linked to the key variables under study and could act as confounders.

Observational studies, even those that use a longitudinal design, cannot determine causality. Nevertheless, because the temporal order between variables is a necessary condition for demonstrating causality,²³ we used an analytic strategy that takes into account the temporal sequencing of key variables in the model, that is, traumatic events, PTSD, and drug use disorder. The analysis can rule out some hypotheses in favor of the plausibility of alternative hypotheses. For example, evidence that PTSD signals increased risk of drug use disorder but that the converse is not true would dampen the plausibility of drug use disorder as a cause of PTSD and strengthen the plausibility that the influence is in the opposite direction.

RESULTS

PREVALENCE OF PTSD AND DRUG A/D

Of the 1007 respondents in our sample, 540 reported a traumatic event based on the combined lifetime data gathered at baseline and follow-up interviews. Of the 540 exposed, 117 (21.7%) met criteria for PTSD, yielding an overall lifetime prevalence of 11.6% in the total sample. There were 140 respondents (prevalence, 13.9%) with a lifetime history of any drug A/D. Of these, 98 had marijuana A/D (prevalence, 9.7%), 45 had cocaine A/D (prevalence, 4.5%), and 28 had prescribed drug A/D (prevalence, 2.8%).

Table 2. Relative Hazards of Drug Abuse or Dependence by Preexisting PTSD, Major Depression, and Conduct Problems*

	Relative Hazard	95% Confidence Interval
Early conduct problems (per problem)†	1.5	1.3-1.6
Depression without previous PTSD‡	2.9	1.5-5.4
PTSD without previous depression‡	4.0	2.3-7.1
PTSD with previous depression‡	7.6	3.1-18.4

*Estimates adjusted for sex, race, and education. PTSD indicates posttraumatic stress disorder.

†The reference group had no early conduct problems.

‡The reference group had no previous depression or PTSD.

DOES PTSD INCREASE THE RISK OF DRUG A/D?

Results showed that PTSD was associated with an increased risk of subsequent drug A/D. Adjusted for race, sex, and education, persons with a history of PTSD had a 4.5-fold increase in the risk of drug A/D compared with those who were not exposed to a traumatic event (95% confidence interval [CI], 2.6-7.6). Persons with a history of exposure without PTSD showed no increased risk of drug A/D (hazards ratio [HR], 1.3; 95% CI, 0.8-2.0). Analysis that stratified by sex produced similar results for men and women.

Another model was estimated to determine whether the observed association of PTSD with drug A/D held when controlling for early conduct problems and preexisting major depression. Three time-dependent covariates were used to represent the onset of PTSD and major depression (depression before PTSD, PTSD without previous depression, and PTSD with previous depression), and the number of early conduct problems was added as a fixed covariate (**Table 2**). Early conduct problems and preexisting depression signaled increased risk of drug A/D. However, even when these factors were controlled, PTSD remained strongly associated with drug A/D. Specifically, PTSD without previous depression signaled a 4-fold increase in the risk of drug A/D. Furthermore, the risk for drug A/D in persons with PTSD after the onset of depression was markedly higher than in persons with depression alone (HR, 7.6 vs 2.9), suggesting independent contributions of PTSD and depression to the risk of drug A/D.

We tested for the possibility that alcohol disorder might confound the observed relationship between PTSD and drug A/D. Posttraumatic stress disorder with and without preexisting alcohol A/D signaled a 4-fold increase in the risk of drug A/D (HR, 4.0 and 3.9, respectively) relative to those with neither PTSD nor alcohol A/D.

RISK OF ABUSE OR DEPENDENCE FOR SPECIFIC DRUGS

Table 3 shows lifetime associations with PTSD across all types of drugs. The strongest association was for abuse or dependence of prescribed drugs. Separate Cox proportional hazards models estimated the risk for subsequent onset of abuse or dependence of specific drugs re-

Table 3. Prevalence and Odds Ratio (OR) of Drug Abuse or Dependence by Lifetime History of PTSD*

Abuse or Dependence	PTSD (n = 117)	No PTSD (n = 890)	OR (95% CI)
Any drug	29.1	11.9	3.0 (2.0-4.7)
Marijuana	14.5	9.1	1.4 (0.8-2.5)
Cocaine	8.6	3.9	2.3 (1.1-4.7)
Prescribed drug†	12.0	1.6	8.5 (3.9-18.3)

*Data for PTSD and no PTSD are given as percentages. PTSD indicates posttraumatic stress disorder; CI, confidence interval.

†The prescribed psychoactive drugs include the use of stimulants, sedatives, or tranquilizers, and opiates other than heroin on one's own to get high or the use of tranquilizers, sedatives, analgesics, antidepressants, or headache medicine as prescribed by a physician.

lated to previous PTSD and exposure without PTSD (**Table 4**). The hazards ratios for marijuana and cocaine A/D were small and not statistically significant ($P = .64$ and $P = .24$, for marijuana and cocaine, respectively). In contrast, PTSD signaled a high risk of prescribed drug A/D (HR, 13.0; 95% CI, 5.3-32.0). We repeated this analysis separating prescribed drug A/D into 2 categories: extramedical (n = 13) and used as prescribed (n = 16). Preexisting PTSD signaled an increased risk of prescribed drug A/D owing to extramedical use (HR, 6.4; 95% CI, 1.6-26.4) and use as prescribed (HR, 24.5; 95% CI, 6.4-93.7). The wide confidence intervals reflect the small number of cases of prescribed drug A/D; nevertheless, the lower bounds of these confidence intervals were well above the null value.

DOES DRUG A/D INCREASE THE RISK OF EXPOSURE AND OF PTSD AFTER EXPOSURE?

The hazard of exposure to a traumatic event was identical for those with and without preexisting drug A/D (HR, 1.0; 95% CI, 0.7-1.4). A model that used a time-dependent covariate to account also for the remission of drug A/D yielded similar results.

To study the hypothesis that drug A/D increases the vulnerability to PTSD following exposure to a traumatic event, we focused on the 540 respondents who had been exposed to traumatic events. Drug A/D signaled a small increase in the risk of PTSD after exposure (HR, 1.6), and the confidence interval included the null value (95% CI, 0.9-2.9). Accounting also for the remission of drug A/D yielded a similar estimate.

COMMENT

The analysis indicates that preexisting PTSD increases the risk of drug A/D, which was the greatest for prescribed psychoactive drugs. There was no evidence that drug A/D increases the risk of exposure to traumatic events. Preexisting drug A/D signaled a slight (not significant) increase in the likelihood that PTSD would develop after a traumatic event. In addition, we found no evidence that exposure to traumatic events in the absence of subsequent PTSD increases the risk of drug A/D. Although this study provides support for the self-

Table 4. Relative Hazards of Specified Drug Abuse or Dependence by Previous Exposure to Traumatic Events and PTSD as Estimated in 4 Cox Proportional Hazards Models*

Abuse or Dependence	Relative Hazards (95% CI)	
	Traumatic Event, No PTSD	PTSD
Any drug	1.3 (0.8-2.0)	4.5 (2.6-7.6)
Marijuana	1.6 (0.9-2.6)	1.8 (0.6-4.9)
Cocaine	0.8 (0.4-1.8)	1.6 (0.6-4.7)
Prescribed drug†	1.8 (0.6-5.2)	13.0 (5.3-32.0)

*Estimates adjusted for sex, race, and education. Hazards are estimated relative to those with no previous exposure to traumatic events or PTSD. PTSD indicates posttraumatic stress disorder; CI, confidence interval.

†See the second footnote to Table 3 for a description of prescribed drug abuse or dependence.

medication hypothesis, our findings also are consistent with the possibility of a shared vulnerability for drug A/D and PTSD after a traumatic event.

The finding that preexisting PTSD increased the risk of subsequent onset of drug A/D is consistent with results from other studies with population-based samples.^{2,6} Breslau et al⁶ found that women with PTSD had more than twice the risk of illicit drug A/D as those without PTSD. Kessler et al² found that PTSD generally was the primary disorder among those with comorbid PTSD and substance use disorders. In addition, our finding that traumatic experiences in the absence of PTSD did not increase the risk of drug A/D is consistent with results from McFall et al,²⁹ who found no difference in the severity of substance use disorders between Vietnam veterans exposed and not exposed to combat but did find that veterans with PTSD had more severe drug problems.

New in this study is the finding that PTSD signaled a high risk of abuse or dependence of prescribed psychoactive drugs but no significant increase in the risk for more commonly used drugs, such as marijuana and cocaine. The strongest association with preexisting PTSD was found in relation to abuse or dependence of psychoactive drugs used as prescribed. This finding suggests that PTSD increases the risk of complications due to prescribed psychoactive medications. However, we do not know whether these drugs were prescribed to treat PTSD or other psychiatric symptoms. In addition, the degree to which the increased risk of prescribed psychoactive drug A/D is specific to PTSD is an area for future research.

We have focused on substance use disorders rather than substance use, and defined *onset* as the age of the first problem of substance abuse or dependence, which occurs later than the onset of drug use. In a study that focused on drug use, Cottler et al¹⁷ found that the age at first drug use typically preceded the age of onset of PTSD and suggested a "possible premorbid vulnerability to PTSD among drug users." Their conclusion was based on the finding that, among those with PTSD and drug use, drug use typically precedes the onset of PTSD. However, a comparison of ages of onset, which focuses only on persons with a history of PTSD who also used drugs, provides no information about the risk of PTSD after the initiation of drug use or vice versa. In contrast, Cox proportional

hazards models with time-dependent covariates enable comparisons of risk. In addition, because Cottler et al¹⁷ did not separate drug users from those with drug A/D, it was impossible to distinguish whether PTSD was more likely to develop in drug users or only in those among them with drug A/D.

Our findings should be considered in light of several limitations. The age range of the sample was restricted to 21 to 30 years of age at the start of the study, so that the maximum age at follow-up was 35 years. Consequently, we cannot extrapolate the findings beyond this age. Although the sample was generally representative of the geographic area, there was some underrepresentation of the extreme ends of the socioeconomic distribution. In our analysis of data collected for this study, we combined baseline and follow-up data and relied heavily on lifetime data collected at baseline. On the other hand, the young age of the cohort should minimize inaccuracy in reporting ages of onset.

Because we found no evidence that traumatic exposure in the absence of PTSD increased the risk of drug A/D, it seems that PTSD, rather than the traumatic experience itself, might be a causal factor in drug A/D. An alternative explanation is that an underlying factor that influences the vulnerability to PTSD after exposure also influences the development of drug A/D. When we controlled for 2 such suspected factors, early conduct problems and major depression, we found that PTSD independently was linked to subsequent drug A/D. In addition, evidence of a pathway in the opposite direction, that is, from drug A/D to PTSD, was relatively weak, diminishing the plausibility of a shared vulnerability to PTSD and drug A/D.

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