

Risk Factors

POSTTRAUMATIC STRESS DISORDER INCREASES RISK FOR SUICIDE ATTEMPT IN ADULTS WITH RECURRENT MAJOR DEPRESSION

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Background: *Genetics of Recurrent Early-Onset Depression study (GenRED II) data were used to examine the relationship between posttraumatic stress disorder (PTSD) and attempted suicide in a population of 1,433 individuals with recurrent early-onset major depressive disorder (MDD). We tested the hypothesis that PTSD resulting from assaultive trauma increases risk for attempted suicide among individuals with recurrent MDD. Methods:* Data on lifetime trauma exposures and clinical symptoms were collected using the Diagnostic Interview for Genetic Studies version 3.0 and best estimate diagnoses of MDD, PTSD, and other DSM-IV Axis I disorders were reported with best estimated age of onset. **Results:** *The lifetime prevalence of suicide attempt in this sample was 28%. Lifetime PTSD was diagnosed in 205 (14.3%) participants. We used discrete time-survival analyses to take into account timing in the PTSD-suicide attempt relationship while adjusting for demographic variables (gender, race, age, and education level) and comorbid diagnoses prior to trauma exposure. PTSD was an independent predictor of subsequent suicide attempt (HR = 2.5, 95% CI: 1.6, 3.8; P < .0001). Neither assaultive nor nonassaultive trauma without PTSD significantly predicted subsequent suicide attempt after Bonferroni correction. The association between PTSD and subsequent suicide attempt was driven by traumatic events involving assaultive violence (HR = 1.7, 95% CI: 1.3, 2.2; P < .0001). Conclusions:* Among those with recurrent MDD, PTSD appears to be a vulnerability marker of maladaptive responses to traumatic events and an independent risk factor for attempted suicide. Additional studies examining differences between those with and without PTSD on biological measures might shed light on this potential vulnerability. *Depression and Anxiety 30:940–946, 2013.* © 2013 Wiley Periodicals, Inc.

Key words: PTSD/posttraumatic stress disorder; suicide/self harm; depression; anxiety/anxiety disorders; trauma

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Suicide is a leading cause of death worldwide. In the United States in 2010, there were 38,364 suicides, an increase over the year before, which continued a trend of recent increases in a rate that had remained relatively flat for over a decade.^[1] Although suicide typically has a multidetermined etiology, nonfatal suicidal behaviors and mental disorders are the strongest and most consistent risk factors of suicide.^[2,3] A recent cross-sectional study found that depression contributes the greatest population attributable risk for suicide attempt of all Axis I or Axis II disorders, accounting for an estimated 40% of attempts.^[4] However, the lifetime prevalence of major depressive disorder (MDD) is high, ranging between 15 and 17% in the United States, and not all, nor even most, patients with depression will go on to make a suicide attempt.

Depression and posttraumatic stress disorder (PTSD) are frequently comorbid, the presence of one increases the risk of the other, and both are associated with attempted suicide.^[5] Using a large epidemiological sample of young adults followed from first grade, Wilcox and colleagues^[6] investigated the impact of exposure to traumatic events on subsequent suicide attempts, separating trauma-exposed persons who developed PTSD from trauma-exposed persons who did not develop PTSD.^[6] We found that PTSD following a traumatic event was an independent predictor of suicide attempt whereas exposure to traumatic events without PTSD was not associated with a later suicide attempt.^[6] A meta-analysis of the association between PTSD and suicidality (suicidal thoughts, behaviors, plans, attempts, and suicides) found the PTSD-suicidality association persisted across studies using different measures of suicidality, current and lifetime PTSD, psychiatric and nonpsychiatric samples, and PTSD populations exposed to different types of traumas.^[7] The association between PTSD and suicide attempt was also independent of sex and age.

Suicide risk could be higher in those with PTSD due to the symptoms of PTSD (e.g., intrusive memories, irritability/anger, and poor impulse control) and/or commonly comorbid psychiatric conditions (e.g., MDD, drug, and alcohol misuse) Oquendo and colleagues^[8] suggested a synergistic effect on suicidal behavior among patients with diagnoses of both PTSD and major depressive episode, and reported that depressed patients with current PTSD had higher lifetime aggression scores than depressed patients without PTSD. Using a large cross-national sample from the World Mental Health Surveys, Nock and colleagues^[9] found that disorders characterized by anxiety and poor impulse control (especially PTSD) emerged as the strongest predictors of which ideators make suicide plans and attempts, and were especially useful in the prediction of unplanned attempts. A diagnosis of depression alone is not especially predictive in determining who is likely to attempt suicide. However, among those with a diagnosis of depression, PTSD predicts which people go on to make a suicide attempt. As Nock and colleagues^[9] point out, depres-

sion leads to the desire to attempt suicide, but disorders characterized by anxiety, agitation, and impulsivity may lead to greater likelihood of acting on thoughts of suicide. Using the same data, Stein and colleagues^[10] found that assaultive violence (e.g., sexual assault, physical assault) conferred the greatest risk of subsequent suicide attempt among traumatic exposures. In contrast to the previous work by Wilcox and colleagues (2009), Stein et al.^[10] found that the relationships between traumatic events and suicidal behavior held irrespective of whether or not PTSD was present.

Cogle et al.^[11] found, using a national household probability sample of women ($n = 3,085$), that only 16% of women with lifetime suicide attempts did not have a history of MDD or PTSD, highlighting the importance of these variables when assessing suicide risk. This group reported that PTSD appeared especially important in predicting suicide attempts as the comorbid diagnosis and PTSD-only groups displayed greater prevalence of suicide attempts than those with MDD only.

In this study, the main aim is to estimate the strength of a suspected causal association that links earlier PTSD to later suicide attempt in a large sample of individuals with recurrent early onset depression, while adjusting for other psychiatric disorders and sociodemographic characteristics. Additionally, we explore the possibility of a differential impact of trauma type (assaultive violence vs. other traumas that do not involve assaultive violence) on attempted suicide. We hypothesize that: (1) PTSD will be an independent predictor of subsequent suicide attempt; and (2) Greater suicide attempt risk will be conferred by PTSD associated with assaultive violence than by PTSD associated with nonassaultive trauma.

METHODS

We conducted an analysis of data collected at six sites during the second iteration of the Genetics of Recurrent Early Onset Depression Study (GenRED II). Recruiting and data collection for GenRED II have been described elsewhere.^[12] Briefly, participants were recruited opportunistically in clinical settings or through advertisement in print media or on the Internet. Participants were interviewed by trained interviewers using the Diagnostic Interview for Genetic Studies version 3.0 (<http://www.nimhgenetics.org>) and the Family Interview for Genetics Studies (<http://zork.wustl.edu/nimh>). Interviewers also obtained information from medical records and through interviews with family members when necessary. Two independent, expert reviewers achieved consensus using DIGS data, medical records, and a narrative summary prepared by the interviewer in order to reach DSM-IV diagnoses, including age at onset and rater confidence levels as well as number of major depressive, manic, or hypomanic episodes, ratings of severity, chronic versus remitting course, and temporal relationship to substance use. Discrepancies between reviewer assessments were settled using a third reviewer. GenRED II subjects were included in this study if they received a best-estimate diagnosis of recurring MDD with at least two lifetime major depressive episodes, onset before age 31 (or a single episode of major depression that lasted 3 years and began before age 31), at least one sibling or parent with recurrent MDD with onset before age 41, MDD

independent of substance dependence (i.e., no lifetime dependence, MDD before dependence, or MDD after at least 2 years of remission from dependence), no diagnosis of bipolar or schizoaffective disorder or schizophrenia, and no suspected bipolar-I disorder in a parent or sibling. The rationale for the recruitment criteria was to ascertain a more genetically homogenous sample to identify risk genes for MDD. Affected relatives were required to have recurrent MDD with age at onset of less than 41 years because Weissman et al. found that, for probands with age of onset in the twenties or earlier, relatives' cumulative risk increases at least to age 40.^[13] All protocols were approved by local institutional review boards, and after a complete description of the study to each subject, written informed consent was obtained.

As in Breslau et al.^[14] and Wilcox et al.^[6], traumatic events were grouped into two broad categories: events that involve assaultive violence and those that do not. The first category, assaultive violence, included personally experiencing physical assault (e.g., being attacked, hit, slapped, kicked, beaten), assault with a weapon (e.g., being shot, stabbed, threatened), sexual assault (e.g., rape, attempted rape, made to perform any type of sexual act), other unwanted or uncomfortable sexual experience, combat or exposure to a war zone in the military or as a civilian, captivity (e.g., being kidnapped, abducted, held hostage, prisoner of war). All other event types were included in the nonassaultive trauma category. These included experiencing a natural disaster (e.g., flood, hurricane, tornado, earthquake), fire or explosion, transportation accident (e.g., car, boat or train accident), serious accident at work, home, or during recreational activity, exposure to toxic substances (e.g., dangerous chemicals, radiation), life threatening illness or injury, witnessing severe human suffering, witnessing sudden, violent death (e.g., homicide, suicide), serious injury, harm, or death you caused to someone else, witnessing any of the assaultive violence events (not personally experiencing them). For each event endorsed, respondents were asked the age when it was first experienced.

All statistical analyses were conducted using Stata 11.^[15] Suicide attempt status was studied using chi-squared analyses according to gender, race (Caucasian [nonminority race/ethnicity] versus minority [other self-reported race/ethnicity]), age group (19–29, 30–39, 40–49, >50 years) and education level (high school or less, college, advanced studies), both overall and among groups of participants with no trauma exposure, with trauma exposure but without PTSD, and with PTSD. Bivariate and multivariate logistic regression models were conducted for descriptive analyses. We sought to account for temporal relationships because traumatic experiences could possibly initiate or worsen psychiatric symptoms, and because depression and other psychiatric morbidity may make one more likely to experience traumatic events or to react more negatively to those experiences. To examine temporal relationships between trauma exposure, PTSD, and suicide attempt, while controlling for confounding risk factors, we constructed several discrete time survival models employing time-varying covariates. The impact of (1) assaultive trauma exposure without PTSD, (2) nonassaultive trauma exposure without PTSD, and (3) PTSD on suicide attempt was assessed using time-varying variables.

PTSD and exposure to assaultive or nonassaultive trauma were coded as time-varying binary variables based on estimated age of onset or first reported traumatic exposure. The models were adjusted for psychiatric comorbidity, also using time-varying variables, which accounted for alcohol abuse and dependence (AAD), drug abuse and dependence (DAD), anxiety disorders excluding PTSD (agoraphobia without panic disorder, panic disorders, trichotillomania, obsessive compulsive disorder, generalized anxiety disorder, social phobia, specific phobia and anxiety NOS) and major depressive episodes (MDE) occurring prior to the first trauma exposure. A second set of discrete time survival models was constructed to explore the differential contribution of type of traumatic exposure (i.e., involving assaultive violence or nonassaultive traumas) and risk of suicide attempt in individuals

with a history of PTSD. Participants with missing values for age, age at onset of any diagnosed disorder, or age of suicide attempt were excluded.

RESULTS

The study population was 83% female and 91% Caucasian with a mean age of 39 at the time of interview. Of the 1,433 participants, 402 (28%) had a history of attempted suicide. Among demographic variables, only lower education level was associated with suicide attempt ($\chi^2 = 13.4, P = .001$). The majority of participants ($n = 1,221, 85\%$) reported experiencing one or more lifetime traumatic life events, and 205 participants (14% of the entire sample) received a best-estimate diagnosis of PTSD (Table 1). Trauma exposure did not vary significantly by race, or education level, although women were more likely to have experienced trauma ($\chi^2 = 34.09; P = .043$). Only minority status ($\chi^2 = 16.9, P = .002$) was associated with increased prevalence of lifetime PTSD diagnosis.

Figure 1 shows Kaplan–Meier cumulative incidence curves comparing the estimated probability of suicide attempt by subgroups of the study population, distinguished by trauma and PTSD history. Participants without a history of trauma exposure exhibited the lowest risk of suicide attempt at 16% ($n = 33$ out of 212), while the trauma-exposed population showed a prevalence of suicide attempt of 28% ($n = 281$ out of 1,016). However, the subset of participants with a lifetime history of PTSD exhibited the greatest risk of suicide attempt with 88 of 205 participants (43%) reporting an attempt. Using bivariate logistic regression, we found, as expected, that a number of psychiatric comorbidities were significantly associated ($P < 0.05$) with having attempted suicide, including anxiety disorders, drug abuse disorders and alcohol abuse disorders (data not shown).

Because timing of trauma exposure and disease onset are so important to establishing causality, we sought to estimate the risk of a suicide attempt subsequent to PTSD and exposure to assaultive and nonassaultive events without PTSD using discrete time survival models (Table 2). The reference group was defined as all persons who did not experience a traumatic event up to that time. The results from the unadjusted model (Model 1) show that neither assaultive nor nonassaultive traumatic events alone, without PTSD, were associated with increased risk of a subsequent suicide attempt. In all subsequent models (Models 2–7) adjusting for demographic characteristics and the presence of MDE, AAD, DAD, and anxiety disorders other than PTSD prior to trauma exposure, nonassaultive violence exposure without PTSD was not associated with suicide attempt. Exposure to assaultive trauma without PTSD was significantly associated with subsequent suicide attempt by conventional standards ($P < .05$) in models 3 and 7, which adjust for a major depressive episode prior to trauma exposure and marginally statistically significant ($P = .066$) in model 6 adjusting for an anxiety disorder

TABLE 1. Lifetime suicide attempt and traumatic exposure across subgroups of the sample population

Characteristics	n (%)					
	No trauma exposure (n = 212; 15%)		Trauma exposure without PTSD (n = 1016; 71%)		PTSD (n = 205; 14%)	
	No attempt (n = 179)	Attempt (n = 33)	No attempt (n = 735)	Attempt (n = 281)	No attempt (n = 117)	Attempt (n = 88)
Gender						
Female	138 (83)	27 (17)	615 (73)	229 (27)	102 (68)	75 (42)
Male	41 (87)	6 (13)	120 (70)	52 (30)	15 (54)	13 (46)
Race						
Minority	19 (90)	2 (10)	46 (60)	28 (40)	17 (50)	14 (50)
Non-Minority	160 (80)	31 (20)	689 (73)	253 (27)	100 (57)	74 (43)
Age						
19–29	79 (90)	9 (10)	220 (73)	84 (27)	27 (57)	20 (43)
30–39	47 (86)	7 (14)	210 (75)	72 (25)	21 (46)	25 (54)
40–49	24 (75)	8 (25)	140 (69)	64 (31)	38 (61)	24 (39)
> 50	29 (76)	9 (24)	165 (73)	61 (27)	31 (62)	19 (38)
Education						
H.S. or less	18 (82)	4 (18)	61 (67)	32 (33)	8 (47)	9 (53)
College	96 (86)	15 (14)	360 (68)	171 (32)	66 (58)	48 (42)
Adv. Studies	65 (82)	14 (18)	314 (80)	78 (20)	42 (58)	31 (42)

Abbreviation: PTSD, Posttraumatic Stress Disorder.

(other than PTSD) prior to trauma exposure. The only estimates in the series of models that survived Bonferroni correction for multiple testing (i.e., $0.05/7 = P < .007$) were the estimates for PTSD. PTSD following exposure to a traumatic event had a robust and consistent association with a subsequent suicide attempt across the series of models that adjusted for sex, race, and age, as well as pre-existing alcohol use disorders, drug use disorders, other anxiety disorders, and MDE. The estimated relative risk (RR) was 2.5 (95% CI, 1.6, 3.8;

$P < .0001$) for model 7, which adjusted for all covariates (Table 2).

Exposure to assaultive trauma was associated strongly with greater risk for the development of PTSD compared with experiencing only nonassaultive traumatic events (OR = 5.7, $P < .0001$). We therefore incorporated this distinction into a second set of discrete time survival models in order to assess the differential contribution of these types of traumas to suicide attempt risk in individuals with a history of PTSD. To explore

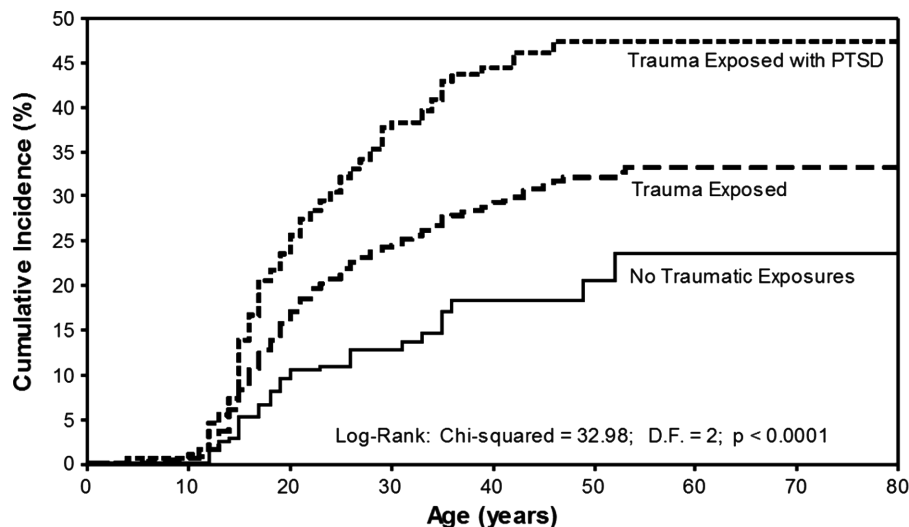


Figure 1. Cumulative incidence of suicide attempt.

TABLE 2. Impact of exposure to nonassaultive violence, assaultive violence, and PTSD on suicide attempts

Predictor	RR (95% CI)	P value
Model 1: Unadjusted		
Assault	1.3 (0.9–1.8)	.229
Non Assault	0.9 (0.6–1.3)	.580
PTSD	2.1 (1.3–3.1)	.001
Model 2: Adjusted for demographics		
Assault	1.4 (0.9–2.0)	.108
Non Assault	0.8 (0.5–1.3)	.393
PTSD	2.0 (1.3–3.0)	.001
Model 3: Adjusted for demographics and MDE		
Assault	1.7 (1.1–2.5)	.012
Non Assault	1.0 (0.7–1.6)	.949
PTSD	2.4 (1.6–3.8)	.0001
MDE	1.4 (1.2–1.2)	.004
Model 4: Adjusted for demographics and AAD		
Assault	1.4 (0.9–2.0)	.103
Non Assault	0.8 (0.6–1.3)	.407
PTSD	2.0 (1.3–3.1)	.001
AAD	1.2 (0.4–3.2)	.764
Model 5: Adjusted for demographics and DAD		
Assault	1.3 (0.9–2.0)	.110
Non Assault	0.8 (0.6–1.3)	.395
PTSD	2.0 (1.3–3.0)	.001
DAD	1.0 (0.3–3.2)	.990
Model 6: Adjusted for demographics and Anxiety Disorder		
Assault	1.4 (1.0–2.1)	.066
Non Assault	0.9 (0.6–1.3)	.539
PTSD	2.1 (1.4–3.2)	.001
Anxiety Disorder	1.3 (0.9–2.0)	.126
Model 7: Adjusted for demographics, AAD, DAD, MDE and Anxiety Disorder		
Assault	1.7 (1.1–2.6)	.011
Non Assault	1.0 (0.7–1.6)	.910
PTSD	2.5 (1.6–3.8)	<.0001
MDE	1.6 (1.1–2.2)	.008
AAD	1.0 (0.3–2.8)	.964
DAD	0.8 (0.2–2.8)	.734
Anxiety Disorder	1.2 (0.8–1.8)	.376

Abbreviation: PTSD, posttraumatic stress disorder; DAD, drug abuse or dependence; MDE, major depressive episode; AAD, alcohol abuse or dependence. Estimates with bold font are statistically significant after Bonferroni correction.

whether the association of PTSD with subsequent suicide attempt differed by the type of event (assaultive vs. nonassaultive) that resulted in PTSD, we conducted survival analysis in the subset of individuals exposed to traumatic events (Table 3). In these models, the reference group was those who were exposed to traumatic events, but did not develop PTSD. Posttraumatic stress disorder caused by exposure to traumatic events that did not involve assaultive violence was not significantly associated with a suicide attempt (estimated RR, 0.9; 95% CI, 0.3–2.4; $P = .84$ for model 7 adjusting for all covariates), whereas PTSD involving assaultive violence had a robust and consistent association with attempted suicide across the series of models (estimated RR, 1.7; 95% CI, 1.3, 2.2; $P < .0001$ for model 7), even after controlling

TABLE 3. PTSD from nonassaultive and assaultive violence exposure on suicide attempts*

Predictor	RR (95% CI)	P value
Model 1: Unadjusted		
Assault with PTSD	1.8 (1.4–2.3)	<.0001
Non assault with PTSD	1.0 (0.4–2.6)	.970
Model 2: Adjusted for demographics		
Assault with PTSD	1.7 (1.3–2.2)	<.0001
Non assault with PTSD	0.9 (0.3–2.5)	.886
Model 3: Adjusted for demographics and MDE		
Assault with PTSD	1.7 (1.3–2.2)	<.0001
Non assault with PTSD	0.9 (0.3–2.5)	.854
MDE	1.3 (0.9–1.7)	.114
Model 4: Adjusted for demographics and AAD		
Assault with PTSD	1.7 (1.3–2.2)	.0001
Non assault with PTSD	0.9 (0.3–2.5)	.884
AAD	0.9 (0.3–2.5)	.884
Model 5: Adjusted for demographics and DAD		
Assault with PTSD	1.7 (1.3–2.2)	.0002
Non assault with PTSD	0.9 (0.3–2.5)	.882
DAD	0.8 (0.2–2.4)	.666
Model 6: Adjusted for demographics and Anxiety Disorder		
Assault with PTSD	1.7 (1.3–2.2)	.0002
Non assault with PTSD	0.9 (0.3–2.5)	.878
Anxiety disorder	1.2 (0.8–1.7)	.410
Model 7: Adjusted for demographics, AAD, DAD, MDE, and Anxiety Disorder		
Assault with PTSD	1.7 (1.3–2.2)	<.0001
Non Assault with PTSD	0.9 (0.3–2.4)	.837
MDE	1.3 (0.9–1.8)	.123
AAD	0.9 (0.3–2.5)	.793
DAD	0.7 (0.2–2.3)	.553
Anxiety disorder	1.1 (0.7–1.6)	.691

for prior MDE. We found no sex differences in the risk of a suicide attempt associated with either event type.

DISCUSSION

This study found that a history of PTSD involving exposure to assaultive violence, within the context of recurrent and early onset depression with a family history, is a strong predictor of a subsequent suicide attempt even after controlling for the presence of psychiatric comorbidity before first exposure to trauma. Meanwhile, nonassaultive violence leading to PTSD was not associated with increased risk of suicide attempt in this sample.

Several limitations of this study should be noted. First, the dataset is cross-sectional and used retrospective report of psychiatric disorders and suicide attempts which could be subject to inaccurate recall and underreporting. Temporal relationships between psychiatric disorders and suicide attempt, however, were sorted out using age of onset of each respective disorder and suicide attempt. The assessment procedures used in this sample, however, are far more elaborate than would be found in epidemiological studies. Second, personality disorders were not studied herein. Oquendo and colleagues^[5] found that comorbid cluster B personality disorders

appear to be a salient factor contributing to greater risk for suicide attempts in patients with a history of MDE who also have PTSD, compared to those with MDE alone. Third, this sample of individuals with recurrent early onset MDD recruited into a genetic study may not be representative of those with MDD. Despite these limitations, the results of this study have important implications for scientific, clinical, and policy efforts aimed at suicide prevention.

The mechanisms in the link between PTSD and suicide attempt need to be further elucidated. Resilience or risk after experiencing assaultive trauma could be related to genetic factors, such as those related to the hypothalamic-pituitary-adrenal (HPA) axis. Some data suggest that trauma exposure and variation in HPA axis genes, such as *FKBP5*^[16] and *CRHBP*^[17] may interact to increase the risk of attempting suicide. It is also possible that epigenetic mechanisms involved in trauma may influence this pathway. Decreased expression of the glucocorticoid receptor, along with increased DNA methylation of that gene's promoter, has been found in suicide decedents exposed to childhood trauma.^[18] Social and psychological factors such as support and connectedness to one's family and community, and coping ability, could moderate the association.^[7]

All of the PTSD observed in our study occurred in individuals who also had MDD. There is evidence for shared liability between the two disorders.^[19] However, many people in our study did not develop PTSD after trauma. It is possible that the mechanisms that do lead to PTSD in a subset of individuals with mood disorder have a relationship to impulsive aggression^[20] or neuroticism,^[21] which also puts them at high risk for suicidal behavior.

Other groups have found that MDD and comorbid anxiety, other than PTSD, may increase risk for suicide attempt.^[22–24] We assessed the association between other anxiety disorders (i.e., panic disorder with agoraphobia, panic disorder without agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, social phobia, specific phobia, anxiety NOS, agoraphobia without panic) and suicide attempt and did not find statistically significant associations for any except lifetime social phobia that was barely statistically significant ($P = .048$) after adjustment for demographic characteristics and other anxiety disorders. When temporality was constrained and we studied social phobia diagnosed prior to first traumatic event, social phobia was not associated with suicide attempts. Our findings may not generalize to completed suicide as one study found a protective association for PTSD and completed suicide in a sample of depressed older, mostly male veterans.^[25] A potential explanation was provided in another study by high mental health service utilization and income supports provided to patients with depression and PTSD in the VA.^[26] Because PTSD and depression often co-occur, mental health professionals should be aware of the effects that this co-occurrence may have on the risk of future suicidal behaviors. The results underscore the need to assess de-

pressed patients for PTSD to ascertain risk for suicidal attempts. The early detection and treatment of PTSD and MDD could play a pivotal role in the prevention of suicide.

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