Published in final edited form as:

J Behav Med. 2018 April ; 41(2): 261–268. doi:10.1007/s10865-017-9906-3.

Posttraumatic stress disorder due to acute cardiac events and aversive cognitions towards cardiovascular medications

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Abstract

Posttraumatic stress disorder (PTSD) after acute medical events is associated with medication nonadherence. The mechanisms of PTSD-related nonadherence are poorly understood. We tested whether patients with elevated PTSD symptoms induced by suspected acute coronary syndrome (ACS) were more likely to have aversive cognitions towards cardiovascular medications. We enrolled a consecutive cohort of patients who presented to the emergency department with suspected ACS. One month after discharge, ACS-induced PTSD symptoms were assessed using the PTSD Checklist (PCL-S), and patients were asked “how often did” 1) “you miss your heart medication because you did not want to be reminded about your heart problem”; 2) “thinking about your heart medication make you feel nervous or anxious”; and 3) “thinking about your heart medication make you think about your risk for future heart problems.” Logistic regression was used to determine the association between elevated PTSD symptoms and each aversive cognition, adjusting for age, sex, race, ethnicity, education, depression, and ACS status. Of 424 patients included, 15.8% had elevated PTSD symptoms (PCL-S ≥ 34). In adjusted analyses, higher PCL-S scores were associated with missing medications to avoid reminders of heart disease (OR 1.22 per 5-point PCL-S increase, 95%CI 1.07–1.40), as well as anxiety (OR 1.34, 95%CI 1.19–1.51) and thoughts of future risk (OR 1.19, 95%CI 1.08–1.32) when thinking about cardiovascular medications. We concluded that patients with elevated PTSD symptoms following suspected ACS were more likely to report aversive cognitions about their cardiovascular medications, suggesting that medications can act as traumatic reminders of the cardiac event and ongoing risk in this group.

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Compliance with Ethical Standards

Conflict of Interest: Dr. Husain declares that he has no conflict of interest. Dr. Edmondson declares that he has no conflict of interest. Ms. Kautz declares that she has no conflict of interest. Ms. Umland declares that she has no conflict of interest. Dr. Kronish declares that he has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Keywords

PTSD; medication adherence; cardiovascular disease; enduring somatic threat

Introduction

Approximately one out of every eight survivors of acute coronary syndrome (ACS) develops posttraumatic stress disorder (PTSD) (Edmondson et al. 2012). The development of PTSD after ACS is associated with double the risk of mortality and recurrent cardiovascular events (Edmondson et al. 2011). Although the factors linking PTSD with prognosis are not all known, medication nonadherence is more common in patients with PTSD and likely contributes to the association between PTSD and adverse prognosis (Shaffer et al. 2013; Shemesh et al. 2006; Shemesh et al. 2001; Shemesh et al. 2004; Edmondson et al. 2012; Alcantara et al. 2014). While PTSD increases risk of nonadherence to recommended health behaviors, including medication nonadherence, regardless of the trauma experienced, the mechanisms explaining the association between PTSD and medication nonadherence remain poorly understood (Kronish, et al. 2012; Kronish et al. 2014; Newman et al. 2011; Zen et al. 2012; Keuroghlian et al. 2011).

The Enduring Somatic Threat (EST) model postulates that, among patients with ACS-induced PTSD, cardiovascular medications may serve as psychologically distressing reminders of the life-threatening cardiac condition that persists after the acute event (Edmondson 2014; Meli, et al. 2017). Indeed, cognitive and behavioral avoidance of reminders of trauma is a hallmark of PTSD (Yehuda 2002; APA DSM-5 Task Force. 2013). Prior research supports this hypothesis indirectly, in that the relationship between PTSD and medication nonadherence has been partly explained by greater death anxiety, high avoidance scores, and greater general concerns about medications (Edmondson et al. 2013; Safren, Gershuny, and Hendriksen 2003; Shemesh et al. 2000).

The objective of this study was to evaluate the association between PTSD symptoms due to a suspected ACS event and aversive cognitions towards cardiovascular medications. We hypothesized that the development of PTSD symptoms would be associated with increased risk for aversive medication-related cognitions.

Methods

The REactions to Acute Care and Hospitalization (REACH) study is an ongoing observational cohort study assessing PTSD in a consecutive sample of patients presenting to the emergency department (ED) of a large, urban, tertiary care hospital (Columbia University Medical Center, New York, NY) for evaluation of suspected ACS. Patients were eligible if they were aged 18 years or older, fluent in English or Spanish, and had a provisional diagnosis of probable ACS (unstable angina or myocardial infarction) as determined by the treating ED physicians. The current study is a pre-planned exploratory analysis including the first 1000 enrolled participants out of a target total 1741 participants in the REACH study. Enrollment for the REACH study was ongoing at the time of this analysis. Given the exploratory nature of the current analysis, no power calculation was

considered to separately determine a sample size goal. Of the first 1639 eligible patients approached, 1000 (61%) consented to participation and were enrolled in the study; no further information was collected about patients who declined study enrollment. Because the aversive medication cognitions questions were not initially included in the 1-month follow up questionnaire, a total of 576 of these participants (58% of first 1000 participants enrolled) were excluded from this analysis because they either A) completed 1-month follow up but were not asked these questions (52% of excluded participants), B) were not yet due 1-month follow up at the time of this analysis (24% of excluded participants), C) had dropout, loss to follow up, death before 1-month follow up (14% of excluded participants), or D) did not answer these questions at 1-month follow up (10% of excluded participants). This yielded a final sample of 424 participants for the current analysis. All procedures performed were approved by CUMC's Institutional Review Board. Informed consent was obtained from all patients. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Measures

PTSD symptoms—*PTSD symptoms* were assessed 1-month after hospitalization using the PTSD Checklist for a Specific Stressor (PCL-S) (Weathers et al. 1993; Blanchard et al. 1996). Patients rated the extent to which they were bothered by 17 PTSD symptoms in response to the “heart problem, emergency room visit, and hospitalization that occurred one month ago when you enrolled in the study.” A PCL score ≥ 34 , commonly used as a screening cutoff, was used to indicate elevated symptoms of post-traumatic stress (henceforth referred to as “elevated PTSD symptoms” for brevity). (Bliese et al. 2008; Creamer, Bell, and Failla 2003; PTSD 2012).

Aversive Cognitions towards Cardiovascular Medications—*Aversive Cognitions towards Cardiovascular Medications* were assessed at 1 month by asking patients: “How often did” 1) “you miss your heart medication because you **did not want to be reminded** of your heart problem”, 2) “thinking about your heart medication make you **feel nervous or anxious**”, and 3) “thinking about your heart medication make you **think about your risk for future heart problems**.” Patients responded using a five-point Likert scale (“never,” “a little of the time,” “some of the time,” “most of the time,” “all of the time”) and patients who reported having the cognition at least “a little of the time” were categorized as having the aversive medication cognition. These items were based directly on the Enduring Somatic Threat theory framework (Edmondson 2014; Meli L 2017).

Covariates

Demographic and comorbidity factors—Age, sex, race, and ethnicity were obtained at enrollment through patient interview. Medical comorbidities were assessed via chart review and used to calculate the Charlson Comorbidity Index, a weighted score from 0–37 for which a higher value indicates increased 1-year mortality risk (Charlson et al. 1994).

ACS status—Although all patients were being evaluated for suspected ACS at enrollment, only some had a confirmed ACS diagnosis upon completion of diagnostic evaluation. Two

medically-trained study personnel blinded to PTSD symptom status classified ACS status by reviewing the complete hospitalization records. Differences in categorization were reconciled through consensus.

Depression—Depressive symptoms in the two weeks prior to enrollment were assessed at the time of study enrollment using the Patient Health Questionnaire (PHQ-8), a self-report instrument with excellent psychometric properties (Kroenke, Spitzer, and Williams 2001; Kroenke et al. 2009).

Statistical Analysis

All patients who completed PTSD symptom screening and questions regarding medication cognitions were included in the current analysis. Descriptive statistics were used to compare the demographic and medical characteristics of patients with and without elevated PTSD symptoms (PCL-S ≥ 34) at 1-month (Bliese et al. 2008; Creamer, Bell, and Failla 2003; PTSD 2012) (t-tests for continuous variables, and χ^2 for categorical variables). Logistic regression was used to calculate odds ratios and 95% confidence intervals for the association between PTSD symptoms (PCL-S score) and each aversive cognition, before and after adjusting for age, sex, ethnicity, race, Charlson index, ACS status, and baseline depressive symptoms. A sensitivity analysis was performed including only patients with confirmed ACS. All analyses were conducted using Stata v14.2 (StataCorp, College Station, Texas).

Results

Between November 2013 and January 2016, we identified 424 patients eligible for this analysis. Patients had a mean age of 62.3 ± 12.8 years and 47% were women. One quarter of patients had elevated depressive symptoms at baseline. A diagnosis of ACS was confirmed in 36% of patients. At 1 month, 15.8% had elevated PTSD symptoms (PCL-S ≥ 34). Compared to patients without elevated PTSD symptoms (PCL-S < 34), these patients were more likely to be younger, female, and to have elevated depressive symptoms (Table 1).

The most frequently endorsed aversive cognition about cardiovascular medications was that medications caused thoughts of future cardiac risk (30% of patients), followed by medications induced feelings of nervousness/anxiety (12%), and served as aversive reminders of their heart problem (8%). Compared to those without elevated PTSD symptoms, those with elevated PTSD symptoms were more likely to report each aversive cognition (each $p < 0.05$; Figure 1).

In unadjusted analyses, higher PCL-S scores were associated with a higher likelihood of reporting each aversive cognition towards cardiovascular medications (Table 2). After adjusting for depression, comorbidity, and demographic characteristics, higher PCL-S scores remained associated with patients reporting that they missed their cardiovascular medications to avoid being reminded of heart disease (OR 1.22 for 5-point increase in PCL-S, 95% CI 1.07–1.40, $p = 0.004$), anxiety caused by thinking about cardiovascular medications (OR 1.34, 95% CI 1.19–1.51, $p < 0.001$), and cardiovascular medications inducing thoughts of future risk (OR 1.24, 95% CI 1.08–1.32, $p = 0.001$). When individual PTSD symptom clusters were examined separately, no differences were noted in the effect

size of the relationship between hyperarousal, avoidant, or intrusive symptoms and any aversive cognition towards medication. In a sensitivity analysis limited to the 154 patients with confirmed ACS, two of these associations remained significant [anxiety when thinking about cardiovascular medications (OR 1.49 for 5-point increase in PCL-S, 95% CI 1.17 – 1.90, $p=0.001$) and cardiovascular medication-induced thoughts of future risk (OR 1.38, 95% CI 1.13 – 1.69, $p=0.002$)]. The association between PTSD symptoms and missing medications to avoid reminders of heart disease in this subgroup was no longer statistically significant (OR 1.15, 95% CI 0.81 – 1.63, $p=0.43$).

Discussion

This is the first study to explicitly demonstrate an association between PTSD symptoms after suspected ACS and aversive cognitions about cardiovascular medications, thereby providing a plausible mechanism linking PTSD with nonadherence to cardiac medications. Specifically, we found that patients with elevated PTSD symptoms after a suspected ACS event were more likely to report having cardiovascular medication-induced feelings of anxiety, to report that the medications induced thoughts of future risk, and to report missing the medications to avoid being reminded of their underlying cardiac disease. These results support the hypothesis that cardiovascular medications, prescribed to reduce patients' risk of a recurrence of the PTSD-inducing ACS event, can ironically serve as triggers for the anxiety, avoidance, and re-experiencing that define PTSD (APA DSM-5 Task Force. 2013).

These results are consistent with previously demonstrated associations between nonadherence and death anxiety, high scores on the PTSD avoidance cluster, and medication concerns related to PTSD after other diagnoses, and also support the previously postulated role of avoidance cognitions as mediators of PTSD-related nonadherence (Cotter 2006; Edmondson et al. 2013; Safren, Gershuny, and Hendriksen 2003; Shemesh et al. 2000). Unlike PTSD after an isolated non-medical traumatic event, PTSD after a medical event such as ACS is caused by an event that portends an *ongoing* risk of mortality (Edmondson 2014; Meli L 2017). Our findings help begin to explain why patients with post-ACS PTSD display a paradoxically increased likelihood of nonadherence to drugs that in fact reduce their risk of recurrent cardiovascular events. It is plausible that aversive cognitions about medications also contribute to the association that has been observed between PTSD and nonadherence after other life-threatening medical events such as stroke, organ transplantation, and the diagnosis of a major illness (e.g. cancer, HIV/AIDS) (Delahanty, Bogart, and Figler 2004; Edmondson et al. 2013; Favaro et al. 2011; Kerkar et al. 2006; Kronish, Edmondson, Goldfinger, et al. 2012; Safren, Gershuny, and Hendriksen 2003; Shemesh et al. 2000). Importantly, we found that the relationship between PTSD symptoms and aversive cognitions towards medications persisted even after controlling for depressive symptoms, even though half of those with elevated PTSD symptoms also reported baseline depressive symptoms. Both diagnoses have been found to be associated with nonadherence in prior studies, and further study is warranted to determine if comorbid depression may also predispose patients with elevated PTSD symptoms to certain aversive medication cognitions.

Notably, the relationship between PTSD symptoms and aversive cognitions towards medications was present despite inclusion of patients eventually found to not have ACS.

This finding supports the notion that it is the cognitive interpretation of increased risk that contributes to the development of PTSD symptoms—and possibly the development of aversive cognitions towards medications—rather than disease severity itself (Chang et al. 2016; Edmondson 2014). It has been demonstrated that among individuals evaluated for ACS, both those determined to have ACS and those not found to have ACS can display elevated levels of perceived threat (White et al. 2017). Similarly, intensive care unit studies have demonstrated no relationship between objectively measured mortality risk (APACHE II or SOFA score) and increased risk for PTSD symptoms (Girard et al. 2007; Patel et al. 2016; Huang et al. 2016). While the association between elevated PTSD symptoms and missing medications to avoid reminders of heart disease was no longer statistically significant in the subgroup of participants with confirmed ACS, we suspect that this is due to a small subgroup sample size of this specific cognition in our exploratory analysis (this was the least common aversive medication cognition overall, and only 9 participants with confirmed ACS admitted to this aversive cognition). However, it is also possible that the phrasing of this question [“How often did you miss your heart medication because...” (emphasis added)] makes participants less likely to report this aversive cognition.

Strengths of our study include our substantial overall sample size, the use of well-validated assessments of PTSD symptoms, and adjustment for potential confounders including depressive symptoms. Limitations included lack of a psychiatric interview to confirm PTSD diagnosis; however, elevated PTSD symptoms irrespective of psychiatric diagnosis have conferred increased cardiovascular risk in prior samples. It should also be noted that self-reported PTSD symptoms may vary based on the setting in which they are assessed. Additionally, we were unable to demonstrate a causal relationship as this was an observational study. We also do not have further information about the 39% of eligible participants that declined to participate in the study, and therefore are unable to assess for any differences between these patients and those included in our analysis that may contribute to selection bias. Limitations also include the use of novel individual questions regarding aversive cognitions towards medications. However, these questions emerged directly from the Enduring Somatic Threat theory. While this study shows that patients with elevated PTSD symptoms had avoidance cognitions that extend to their medications, further research is necessary to expand upon these findings given the exploratory nature of the analysis, including the development of validated measures to better assess the basis of this relationship and eventual confirmation of these findings in the larger study cohort. Further, adherence was not measured in our current study; additional investigations are warranted to confirm whether there is a further association between PTSD-related aversive cognitions towards medications and medication nonadherence. An improved understanding of aversive cognitions towards medications among patients with PTSD symptoms can potentially lead to the development of targeted interventions aimed at promoting positive healthful associations with cardiovascular medications.

In conclusion, we found that patients with PTSD after a suspected ACS event are more likely to report aversive cognitions regarding cardiovascular medications, providing one mechanism to explain PTSD-related nonadherence. Further investigations are warranted to better establish the nature of this relationship and to determine whether interventions to

reduce PTSD symptoms in the post-ACS setting can prevent these aversive cognitions and, in turn, promote improved medication adherence within this vulnerable patient group.

Acknowledgments

Funding: This study was supported by grants from the National Heart, Lung, and Blood Institute (NHLBI) [HL117832 and HL123368]. Dr. Kronish received additional support from NCATS.

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Figure 1.
Frequency of Aversive Cognitions Among Patients With and Without Elevated PTSD Symptoms

Table 1

Patient Characteristics Among Patients With and Without Elevated PTSD Symptoms

Characteristic	All (N=424)	Non-elevated PTSD symptoms (N=357; 84.2%)	Elevated PTSD symptoms (PCL-S 34) (N=67; 15.8%)	P-value
Age in years, mean (SD)	62.3 (12.8)	62.9 (13.2)	59.5 (10.4)	0.05
Female	198 (47%)	159 (45%)	39 (58%)	0.04
Ethnicity				
Hispanic	223 (53%)	193 (54%)	30 (45%)	0.25
Not Hispanic	201 (47%)	164 (46%)	37 (55%)	
Race				
Caucasian	106 (25%)	93 (26%)	13 (19%)	0.24
Black	110 (26%)	88 (25%)	22 (33%)	
Asian	9 (2%)	6 (2%)	3 (4%)	
Other/Multiple/Did not respond	199 (47%)	170 (48%)	29 (43%)	
Education Level				
Less than High School	69 (16%)	62 (17%)	7 (10%)	0.45
Some High School	68 (16%)	55 (15%)	13 (19%)	
High School Diploma/GED	87 (21%)	70 (20%)	17 (25%)	
Trade/Vocational	12 (3%)	11 (3%)	1 (1%)	
Some College	69 (16%)	57 (16%)	12 (18%)	
College Graduate	73 (17%)	60 (17%)	13 (19%)	
Graduate/Professional School	46 (11%)	42 (12%)	4 (6%)	
Marital Status				
Single	119 (29%)	91 (25%)	28 (42%)	0.06
Married/Partner	188 (44%)	168 (47%)	20 (30%)	
Separated	23 (5%)	20 (6%)	3 (4%)	
Widowed	45 (11%)	38 (11%)	7 (10%)	
Divorced	45 (11%)	36 (10%)	9 (13%)	
Charlson Comorbidity Index, mean (SD)	2.0 (2.0)	1.8 (2.0)	2.2 (2.1)	0.32
Baseline Depressive Symptoms (PHQ-8 10)	106 (25%)	72 (20%)	34 (51%)	<0.001
Prior Coronary Artery Disease	144 (34%)	123 (34%)	21 (31%)	0.62
Confirmed Acute Coronary Syndrome	154 (36%)	130 (36%)	24 (36%)	0.93

Data are presented as n, (%) unless otherwise specified.

^y

At least "a little of the time", at 1-month follow up.

Table 2

Association between PTSD Symptoms & Aversive Cognitions about Cardiovascular Medications

A. Missed heart medication to avoid reminder of heart problem (N=406)				
Characteristic	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p*
Elevated PTSD symptoms [†]	1.24 (1.11 – 1.39)	<0.001	1.22 (1.07 – 1.40)	0.004
Age ^{††}	–	–	0.98 (0.95 – 1.01)	0.22
Female [§]	–	–	0.59 (0.26 – 1.36)	0.22
Hispanic Ethnicity ^{§§}	–	–	0.73 (0.42 – 1.26)	0.26
White Race ^{§§§}	–	–	0.28 (0.06 – 1.27)	0.10
High School Graduate ^{†††}	–	–	0.30 (0.13 – 0.69)	0.005
Charlson Comorbidity Index [∫]	–	–	0.88 (0.70 – 1.12)	0.30
Confirmed ACS	–	–	0.77 (0.31 – 1.89)	0.57
Baseline Depression Symptoms ^{∫∫}	–	–	1.39 (0.56 – 3.47)	0.48

B. Thinking about heart medication induced nervousness/anxiety (n=407)				
Characteristic	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p*
Elevated PTSD symptoms [†]	1.36 (1.22 – 1.50)	<0.001	1.34 (1.19 – 1.51)	<0.001
Age ^{††}	–	–	0.97 (0.94 – 1.00)	0.05
Female [§]	–	–	1.08 (0.53 – 2.21)	0.83
Hispanic Ethnicity ^{§§}	–	–	0.97 (0.59 – 1.60)	0.90
White Race ^{§§§}	–	–	0.98 (0.42 – 2.31)	0.97
High School Graduate ^{†††}	–	–	1.41 (0.62 – 3.17)	0.41
Charlson Comorbidity Index [∫]	–	–	0.79 (0.63 – 0.99)	0.04
Confirmed ACS	–	–	2.96 (1.43 – 6.13)	0.004
Baseline Depression Symptoms ^{∫∫}	–	–	2.00 (0.93 – 4.32)	0.08

C. Thinking about heart medication induced thoughts of future risk (n=404)				
Characteristic	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p*
Elevated PTSD symptoms [†]	1.24 (1.13 – 1.35)	<0.001	1.19 (1.08 – 1.32)	0.001
Age ^{††}	–	–	0.97 (0.95 – 0.99)	0.005
Female [§]	–	–	1.11 (0.69 – 1.78)	0.68
Hispanic Ethnicity ^{§§}	–	–	1.12 (0.79 – 1.58)	0.52
White Race ^{§§§}	–	–	0.94 (0.53 – 1.67)	0.84
High School Graduate ^{†††}	–	–	1.33 (0.78 – 2.27)	0.29
Charlson Comorbidity Index [∫]	–	–	0.86 (0.75 – 0.98)	0.02
Confirmed ACS	–	–	1.39 (0.85 – 2.28)	0.19
Baseline Depression Symptoms ^{∫∫}	–	–	2.33 (1.37 – 3.95)	0.002

Abbreviations: PTSD- Post-traumatic Stress Disorder; CAD- Coronary Artery Disease; ACS- Acute Coronary Syndrome; OR- Odds Ratio; CI- Confidence Interval

*
p-values are for adjusted ORs

[†]
per 5-point increase on PCL;

^{††} Per 1 year;

[§] Versus Male;

^{§§} Versus Not Hispanic;

^{§§§} Versus Non-White;

^{†††} Education level High School Graduate or greater Versus education level Less than High School or Some High School;

[∫] Per 1-unit increase;

^{∫∫} PHQ-8 ≥ 10 versus PHQ-8 < 10