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Posttraumatic Stress Disorder and Nonadherence to Medications Prescribed for Chronic Medical Conditions: A Meta-Analysis

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Abstract

Background—Patients with posttraumatic stress disorder (PTSD) are at increased risk for adverse consequences from comorbid medical conditions. Nonadherence to medications prescribed to treat those comorbid conditions may help explain this increased risk. We sought to determine the association between PTSD and medication nonadherence and whether it varied according to the type of event inducing the PTSD.

Methods—Prospective observational cohort or cross-sectional studies relating PTSD and nonadherence among adults prescribed medications for a chronic medical illness were identified by searching MEDLINE, EMBASE, PsycINFO, the Cochrane Library, CINAHL, SCOPUS, and the PILOTS Database and by hand-searching bibliographies from selected articles. Individual estimates of odds ratios were pooled using random effects metaanalysis with inverse variance weighting. Articles were pooled separately according to whether PTSD was induced by a medical versus non-medical event.

Outcomes—Sixteen articles comprising 4483 patients met eligibility criteria. The pooled effect size of the risk of PTSD to medication nonadherence was OR 1.22 (95% CI, 1.06–1.41). Among the 6 studies of medical event-induced PTSD, the OR was 2.08 (95% CI, 1.03–4.18); $p=0.04$. Among the 8 studies in which PTSD was not induced by a medical event, the OR was 1.10 (95% CI, 0.99–1.24); $p=0.09$.

Interpretation—Patients with PTSD were more likely to be nonadherent to medications prescribed for chronic medical conditions – an association that may exist specifically when PTSD was induced by a medical event. Medications may serve as aversive reminders among survivors of acute medical events, magnifying avoidance behaviors characteristic of PTSD.

Introduction

With a lifetime prevalence of posttraumatic stress disorder (PTSD) in the general population of 5–14% (Yehuda, 2002; Kessler et al., 1995), and with an even higher prevalence in patients with comorbid medical conditions, PTSD is a frequently encountered psychiatric condition in primary care settings (Yehuda, 2002; Kessler et al., 1995; Liebschutz et al., 2007; Magruder et al., 2005; Spiro et al., 2006; Lecrubier, 2004; Sripada et al., 2014; Friedman, 2004). Patients with PTSD may be profoundly burdened by disabling psychological distress, elevated risk for suicide, and inability to work (Yehuda, 2002). Furthermore, a growing body of research demonstrates that PTSD, among civilians and veterans alike, increases both the risks and the consequences of comorbid medical conditions (Beckham et al., 1998; Jordan et al., 2011; Wisnivesky et al., 2011; Hoge et al., 2007; Jakupcak et al., 2008; Ahmadi et al., 2011; Pietrzak et al., 2012; Andersen et al., 2010). For example, patients with PTSD after an acute coronary syndrome have nearly twice the risk of recurrent cardiovascular events and mortality (Edmondson et al., 2011; Shemesh et al., 2004), and among patients with diabetes, those with PTSD have poorer glycemic control and worse prognosis (Miller et al., 2011; Trief et al., 2006). The mechanisms explaining the associations between PTSD and adverse outcomes from medical illness remain poorly understood (Dedert et al., 2010). Nonadherence to preventive medications may represent one such mechanism.

Some, but not all, studies have found an association between PTSD and nonadherence to medications prescribed for chronic medical conditions (we define a “chronic medical condition” as a long-lasting and typically progressive, non-psychiatric disease often treated with medications longitudinally to achieve disease control). One prior systematic review assessed the association of various mental disorders including PTSD on adherence to combination antiretroviral medications for human immunodeficiency virus (HIV) (Springer et al., 2012). No quantitative analysis was conducted as part of this review. To our knowledge, no prior meta-analysis has examined the association between PTSD and nonadherence to medications prescribed for a variety of chronic medical conditions. Such a review may help clarify this association. It may also enable us to examine whether the association between PTSD and medication nonadherence varies between different medical conditions – HIV, for example – or by the trauma that triggered PTSD. Compared to patients with PTSD induced by non-medical events, patients with PTSD induced by acute medical events such as stroke or cancer diagnosis may be more likely to be nonadherent because medications may serve as aversive reminders of the traumatic medical event in these patients (Edmondson, 2014). Furthermore, such a review may additionally enable us to examine the method by which medication adherence is measured as a moderator.

Accordingly, we performed a systematic search and meta-analysis of observational studies examining the association between PTSD and nonadherence to medications prescribed for a range of chronic medical conditions. We hypothesized that patients with PTSD would be more likely to be nonadherent to their medications, overall, and that the association between PTSD and medication nonadherence would be stronger when PTSD was triggered by an acute medical event.

Materials and Methods

This meta-analysis aimed to include all evidence from observational studies that have investigated PTSD and nonadherence to medications prescribed for comorbid chronic medical conditions. The protocol for this systematic review was registered in PROSPERO prior to conducting the review (Kronish et al., 2013).

Search Strategy

The research methodology was done in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). With the assistance of an information specialist (L.F.), potentially relevant articles were identified by searching publicly available computerized databases. The search included all articles and abstracts including unpublished doctoral theses referenced from database inception to January 24, 2017, in MEDLINE, EMBASE, PsycINFO, the Cochrane Library, CINAHL, SCOPUS, and the PILOTS Database. All relevant subject headings and free text terms for PTSD and medication adherence were identified and combined with AND. No language restrictions were applied (Appendix 1). Additional studies were sought by searching the reference lists of studies already identified for inclusion following the screening of the electronic database search results.

Study Selection

Articles were eligible for inclusion if they satisfied the following criteria: the authors reported data from an original, peer-reviewed study; the study design was a prospective observational cohort or crosssectional survey; the study population included adults prescribed medications for a chronic medical illness; there was no study intervention to improve adherence (because in these studies all baseline subjects were by definition nonadherent, precluding the extraction of an odds-ratio showing the odds of those subjects being nonadherent); PTSD was measured using a validated self-report instrument or psychiatric interview; adherence was measured using a validated self-report instrument or an objective measure; and the authors reported on the association between PTSD and nonadherence.

Two investigators (R.B., L.W.) independently reviewed all citations identified through the literature search using a predefined protocol that included the eligibility criteria. Articles that clearly did not meet inclusion criteria were excluded at the title and abstract level. The remaining articles were selected for full, English-language text review. When limited information was available from the abstract, full text was obtained. The two investigators (R.B., L.W.) then independently reviewed all full text articles to identify eligible articles.

All eligible articles were assigned a quality rating (poor, fair, good, excellent) by two investigators (E.B., L.W.) using the Methodologic Evaluation of Observational Research (MEVORECH) checklist developed by the Agency for Healthcare Research and Quality (Shamliyan et al., 2011). Key features that determined quality included study design (i.e., prospective observational studies were rated higher than cross-sectional ones), response rate, follow-up rate, duration of follow-up, consideration of confounders in models of the

association of PTSD with adherence, statistical analysis, and generalizability to other study populations. Each of these elements was assigned a grade, and then an overall rating was assigned based on the combination of these elements' scores.

Disagreements regarding the article selection and quality ratings were resolved through discussion with a third reviewer (I.K.) and full consensus was achieved at each stage of review. A study was included in this meta-analysis if there was consensus that it met eligibility criteria and had risk assessments in the format of hazard ratios (HRs) or odds ratios (ORs) or summary statistics that could be converted into HRs or ORs.

Data Extraction

Two investigators (R.B., L.W.) independently extracted data from selected studies using a standardized form. Information was collected regarding study characteristics (study name, authors, publication year, journal, study site, follow-up years, and number of participants), participant characteristics (age, gender, race, ethnicity, education), PTSD assessment (timing of assessment, self-report questionnaire or clinical interview), medication adherence assessment (type of self-report instrument or objective instrument), and analysis strategy (statistical models, lists of covariates in models).

Data Synthesis and Analysis

Eligible studies that included quantitative risk estimates for the association between PTSD and medication nonadherence were pooled. We sought to contact authors to obtain risk estimates when these were unavailable from eligible articles. We pooled articles according to prespecified analyses including type of medical condition and type of traumatic event (medical versus non-medical). We also pooled articles according to their overall quality rating and inclusion of possible confounders in their adjusted analyses. In particular, we pooled studies that included depression as a covariate because depression frequently accompanies PTSD and has been associated with medication nonadherence in prior studies (DiMatteo et al., 2000). Finally, we pooled studies according to method of adherence measurement. Risk estimates were standardized to express odds ratios of nonadherence. Individual estimates of odds ratios were pooled using random effects meta-analysis with inverse variance weighting in Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ). The I-squared statistic was calculated to estimate the percentage of variability across studies that is attributable to heterogeneity, and was tested for deviation from zero. To test for sources of heterogeneity for our primary outcome, we performed mixed-effects subgroup analyses, in which random-effects models were used to combine studies within subgroups, that compared pooled ORs separately for articles by quality assessment (poor, fair, good, or excellent quality); types of patients (e.g., HIV or cardiovascular disease); and PTSD trigger (secondary to an acute medical event versus other). We used chi-square to test for significance in these analyses and log transformed ORs to approximate normality. We assessed for publication bias using visual methods and the fail-safe N.

Results

Literature Search Results

The comprehensive search yielded 2145 studies (Fig. 1). Seventeen studies met initial inclusion criteria, though one (Boarts et al., 2009) did not present a risk assessment in a format that could be converted into HRs or ORs and therefore was not included in the quantitative meta-analysis.

Study and Population Characteristics

The 16 studies included in the quantitative meta-analysis (Table 1) assessed PTSD and nonadherence to medications for chronic medical conditions in 4264 patients. Several different patient populations were represented: human immunodeficiency virus (HIV) (nine studies, 1565 patients) (Boarts et al., 2006; Delahanty et al., 2004; Keuroghlian et al., 2011; Nilsson Schonnesson et al., 2007; Vranceanu et al., 2008; Wagner et al., 2012; Whetten et al., 2013; Halkitis et al., 2014; Saucedo, 2014), myocardial infarction (MI)-survivors (two studies, 213 patients) (Shemesh et al., 2001, 2004), transplant patients (one study, 107 patients) (Favaro et al., 2011), stroke or transient ischemic attack (TIA) survivors (one study, 535 patients) (Kronish et al., 2012a), established cardiovascular disease (CVD) (one study, 1022 patients) (Zen et al., 2012), hypertension (one study, 98 patients) (Kronish et al., 2014), and primary care patients recruited from Department of Veterans Affairs Medical Centers who were prescribed at least one chronic disease medication (one study, 724 patients) (Kronish et al., 2012b).

Assessments of PTSD and Medication Nonadherence

PTSD was measured using either self-report scales (13 studies) or psychiatric interviews (three studies). Self-report scales included the Impact of Event Scale (IES) or its revised version IES-R; the Posttraumatic Diagnostic Scale (PDS); the PTSD Checklist (PCL); the PTSD Checklist – Stressor Specific (PCL-S); the Startle, Physiological arousal to reminders, Anger, and Numbness (SPAN); the Trauma Awareness and Treatment Center (TATC) PTSD Scale; and the Primary Care PTSD screen. Structured psychiatric assessments included the Clinician-Administered PTSD Scale (CAPS), and both the personal and computerized PTSD module of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). The prevalence of PTSD in individual studies, when specified, ranged from 9% (Zen et al., 2012) to 42% (Boarts et al., 2006), with an overall prevalence in of 26.4% among the 11 studies that reported dichotomous PTSD data. The remaining studies provided continuous score assessments of PTSD symptoms.

Medication nonadherence was assessed using objective (versus selfassessment) measures in six studies, including electronic device monitor, pill count, thromboxane production (for aspirin adherence), and determination by the medical team based in part on patients' drug levels. A range of self-report adherence measures were used, including questionnaires taken from the Adult AIDS Clinical Trials Group (AACTG), Medication Adherence Questionnaire, Coronary Artery Risk Development in Young Adults (CARDIA), as well as other questionnaires or visual analog scales. The prevalence of nonadherence in individual studies ranged from 10% (Favaro et al., 2011) to 42% (Keuroghlian et al., 2011), with an

overall prevalence in the metaanalysis sample of 29% among studies that reported nonadherence rates explicitly.

Overall Association of PTSD with Medication Nonadherence

When pooled across all studies, there was an increased risk of nonadherence to chronic disease medications for individuals with PTSD versus those without PTSD (OR 1.22, 95% CI, 1.06–1.41) (Figure 2). There was statistically significant between-study heterogeneity in effect size estimates, ($Q = 59.4$, $p < 0.001$). This supported the use of a random effects model in pooled analyses.

PTSD and Medication Nonadherence According to Type of Trauma

We compared the association of PTSD with risk for nonadherence across studies according to whether PTSD was or was not specifically induced by an acute medical event (Figure 3). Among the six studies of medical event-induced PTSD, the pooled OR was 2.08 (95% CI, 1.03–4.18); $p=0.04$. Among the eight studies in which PTSD was not induced by a medical event, the OR was 1.10 (95% CI, 0.99–1.24); $p=0.09$. There was a trend toward this difference in effect between the two sets of studies being statistically significant ($p = 0.08$). Statistically significant heterogeneity still existed for each subgroup of studies (both p 's < 0.02).

PTSD and Medication Nonadherence According to Medical Condition

Vascular Disease—The largest chronic disease subgroup represented in this meta-analysis was patients with vascular disease: MI-survivors, heart transplant patients, stroke/TIA survivors, patients with established CVD, and patients with hypertension. This subgroup comprises nearly half ($n = 1,975$ or 46%) of the patients in the meta-analysis. The association between PTSD and adherence among the six studies of subjects with vascular disease (2.86, 95% CI = 1.54, 5.29) differed significantly from the 10 studies with subjects who did not have vascular disease (1.14, 95% CI = 1.003, 1.29; Q (between) = 8.22, $p = 0.004$).

HIV—HIV: The second largest chronic disease subgroup was HIV, comprising more than one-third ($n=1565$ or 37%) of the meta-analysis population. We assessed the risk of PTSD on medication nonadherence among HIV versus non-HIV study populations, and found a significant difference between approximated odds for the two populations HIV=1.10, 95% CI=0.97–1.24; non-HIV=2.34, 95% CI=1.40–3.92; Q (between)=7.8, $p=0.005$).

Quality Analysis

Two studies were rated as excellent, 7 as good, 6 as fair, and 1 as poor. The association of PTSD and nonadherence across these studies, though qualitatively different, did not differ significantly from one another (Q (between)=3.2, $p=0.36$). One element of quality that we specifically quantitatively analyzed was studies' inclusion of covariates in their analyses. Most studies ($n=10$) adjusted for at least one potential confounder in their analysis of the effect of PTSD on nonadherence, with potential confounders including age, gender, race/ethnicity, depression, dissociation, income, number of medications, medical comorbidities,

and social support. Seven studies included adjustment for depression. We compared estimates for studies that adjusted for depression versus those that did not, and found that the association among studies that adjusted for depression (1.26, 95% CI=1.0, 1.59) was not significantly different than that among studies that did not adjust for depression (1.26, 95% CI=0.86, 1.85; Q (between)=0, p =0.99). Additionally, we assessed the association between the type of PTSD measure and adherence, and found the association among studies that measured PTSD via psychiatric interview (1.52, 95% CI=1.12, 2.06) was not significantly different from the association among studies that measured PTSD via self-report (1.18, 95% CI=1.02–1.37; Q (between)=2.14, p =0.14). Objective measures of adherence are often viewed as superior to subjective measures. Three studies assessed adherence using an electronic pillbox (Vranceanu et al., 2008; Wagner et al., 2012; Kronish et al., 2014) – the gold standard for measuring the day-to-day implementation of a medication regimen (Zeller et al., 2008; Urquhart, 1997) – one used pill counts conducted by nurses, one measured adherence via serum levels of a prescribed medication, one relied on a physician's assessment, and 10 assessed adherence by self-report. The association between PTSD and adherence among the three studies using an electronic pillbox (1.23, 95% CI=0.73, 2.09) did not significantly differ from the association among the remaining studies (1.27, 95% CI=1.08, 1.49; Q (between)=0.01, p =0.91). The association between PTSD and nonadherence among the 10 studies that assessed adherence by self-report (1.22, 95% CI=1.05–1.42, p =0.011) did not significantly differ from the association among the remaining studies (1.57, CI=0.87–2.86; Q (between)=0.67, p =0.41).

Publication bias

There was some visual evidence of publication bias, such that significant positive associations between PTSD and nonadherence may have been more likely to be published than studies with no or negative association between PTSD and nonadherence (Figure 4). The fail-safe N indicates that 82 additional studies with no association between PTSD and nonadherence would need to exist in order for the odds ratio for the true association between PTSD and medication nonadherence to be 1.

Discussion

To our knowledge, this is the only meta-analysis that examines the association between PTSD and nonadherence to medications prescribed for a variety of chronic medical conditions. The current meta-analysis of 16 observational studies found that there was an increased risk of chronic disease medication nonadherence among subjects with PTSD versus those without PTSD. Furthermore, there was a trend toward this association being more strongly present when PTSD was induced by the experience of the medical disease necessitating medication rather than by non-medical traumatic experiences. Among the six studies of patients with acute medical events, patients with medical event-induced PTSD had nearly twice the odds of being nonadherent to chronic disease medications as compared to patients without PTSD.

PTSD has the potential to impact adherence through several distinct mechanisms rooted in PTSD-specific behavioral and cognitive symptoms. Avoidant behaviors so characteristic of

PTSD may lead patients to not adhere to medications that remind them of their own mortality or specifically of their initial trauma (Shemesh et al., 2004). Avoidance may thus underlie the association between PTSD and skipping medications (Edmondson et al., 2014), especially medication related to the medical event inducing the PTSD. It is also possible that PTSD patients embrace illness or medication beliefs that lead to medication nonadherence (Edmondson et al., 2013; Hekler et al., 2008; Stafford et al., 2008). PTSD has been associated with a sense of lack of personal control over illness (Wikman et al., 2011) or foreshortened future (Greenwell and Cosden, 2009; Rodriguez et al., 2008). Patients may also skip medications out of a sense of futility because they are convinced that the future does not offer the possibility of positive, good events. Appreciating the future impact of medications on asymptomatic but prognostically significant conditions such as hypertension may be particularly challenging in the context of these distinct illness beliefs.

Additionally, patients with PTSD may have cognitive impairments (Stafford et al., 2008; Hekler et al., 2008) that have been linked with medication nonadherence (Lovejoy and Suhr, 2009). For example, PTSD-related deficits in cognitive function may lead to unintentional nonadherence – as many as nearly half of the PTSD patients in a recent study reported regularly forgetting their medications (Edmondson et al., 2014).

As aforementioned, the association between PTSD and medication nonadherence was strongest in the context of medical event-induced PTSD. This association is less clear, however, among the subset of patients who are HIV positive and are diagnosed with HIV-related PTSD. Notably, among studies of HIV patients, the one (Delahanty et al., 2004) that reported the largest and most statistically significant relationship between PTSD and HAART nonadherence focused on PTSD specifically attributed to the diagnosis of HIV rather than to other trauma. However, a subgroup analysis within another (albeit negative) study (Wagner et al., 2012) of HIV patients found no difference in adherence among those who had PTSD largely attributable to their HIV diagnosis versus those who had PTSD due to another trauma. As a result of these conflicting results, the association between HIV-related PTSD and nonadherence will benefit from further investigation.

The findings of our meta-analysis should be interpreted in light of several limitations. The fail-safe N of 82 suggests that our meta-analytic finding may not be robust to publication bias, as a generally accepted rule of thumb for interpreting fail-safe N is that a meta-analytic result is robust to publication bias if $N \geq 5k+10$, where k is the number of studies including in the meta-analysis, and so 100 in this case. It is also important to consider the quality of the published studies included in the meta-analysis. Nearly half of the included studies were rated as poor or fair quality. The number and size of studies limited the ability to determine the influence of some potential moderators, specifically whether the association between PTSD and adherence was influenced by method of measuring adherence or by method of assessing PTSD. Nevertheless, our analysis showed that quality rating did not affect the association between PTSD and chronic disease medication nonadherence.

Overall, this meta-analysis suggests that PTSD is associated with nonadherence to medications prescribed for comorbid chronic medical conditions, specifically among patients for whom PTSD was induced by a medical event. While the mechanisms of the

association need to be further studied, avoidance, fatalistic illness beliefs, or cognitive impairments may underlie the association. PTSD is common even among primary care patient populations, and practitioners should thoughtfully inquire about chronic disease medication nonadherence among patients with PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
PRISMA Flow Diagram

Figure 2.
Risk of nonadherence to chronic disease medications for individuals with versus without PTSD

Figure 3.

The association between PTSD and nonadherence to chronic disease medications according to whether PTSD was induced by an acute medical event

Figure 4.
Funnel plot to assess publication bias across studies.

Table 1
Studies of the Association between Posttraumatic Stress Disorder and Medication Nonadherence (N=16)

Source, year	Study Location	N	PTSD prevalence	PTSD measure	Clinical Interview	Nonadherence Rate	Adherence Measure	Disease Population	Medication
Boarts, 2006	US	57	42.1%	PDS	N	-	self-report from AACTG	HIV	HAART
Delahanty, 2004	US	110	-	IES	N	-	self-report from AACTG	HIV	HAART
Favaro, 2011	Italy	107	13% PTSD	interview /DSM-IV	Y	10%	cardiologist's scores	transplant	immunosuppression
Halkitis, 2015	US	180	-	TATC	N	-	self-report from AACTG	HIV	HAART
Keuroghlian, 2011	US	38	44.7%	IES		42.1%	self-report (1 question from AACTG)	HIV	HAART
Kronish, 2012a	US	724	35%	CAPS	Y	-	self-report from CARDIA	general medicine	any
Kronish, 2012b	US	535	17.8%	PCL-S	N	41%	self-report Morisky survey	stroke/TIA	any
Kronish, 2014	US	98	19%, 21% had intermediate	Primary care PTSD screen	N	41%	electronic pillbox	HTN	anti-HTN
Nilsson, 2007	Sweden	193	28%	IES	N	37%	self-report from AACTG	HIV	HAART
Sauceda, 2014	US	149	-	IES-R	N	-	visual analog scale, categorical labels (ability and frequency), open-ended questions (frequency of missed meds, missed apps)	HIV	HAART
Shemesh, 2001	US, Israel	140	9.8% PTSD intrusion and avoidance symptoms	IES	N	-	pill count by nurse	MI	captopril
Shemesh, 2004	Israel	73	20%	IES	N	16%	labwork: thromboxane production	MI	aspirin
Vranceanu, 2008	US	156	21%	SPAN	N	-	electronic pill bottle cap	HIV	HAART
Wagner, 2012	US	214	38%	PDS	N	-	electronic pill bottle cap	HIV	HAART
Whetten, 2013	Tanzania	468	-	PCL	N	17.30%	three-item self report	HIV	HAART
Zen, 2012	US	1,022	9%	computer DSM-IV	Y	-	self-report	CVD	prescribed meds